



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/415, C07D 409/06</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/36585</b> <b>(43) International Publication Date:</b> 9 October 1997 (09.10.97)												
<b>(21) International Application Number:</b> PCT/US97/06259 <b>(22) International Filing Date:</b> 1 April 1997 (01.04.97)  <b>(30) Priority Data:</b> <table border="0"><tr><td>60/014,592</td><td>3 April 1996 (03.04.96)</td><td>US</td></tr><tr><td>9613462.2</td><td>27 June 1996 (27.06.96)</td><td>GB</td></tr><tr><td>60/022,586</td><td>24 July 1996 (24.07.96)</td><td>US</td></tr><tr><td>9617279.6</td><td>16 August 1996 (16.08.96)</td><td>GB</td></tr></table> <b>(71) Applicant (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> ANTHONY, Neville, J. [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(74) Common Representative:</b> MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		60/014,592	3 April 1996 (03.04.96)	US	9613462.2	27 June 1996 (27.06.96)	GB	60/022,586	24 July 1996 (24.07.96)	US	9617279.6	16 August 1996 (16.08.96)	GB	<b>(81) Designated States:</b> AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
60/014,592	3 April 1996 (03.04.96)	US												
9613462.2	27 June 1996 (27.06.96)	GB												
60/022,586	24 July 1996 (24.07.96)	US												
9617279.6	16 August 1996 (16.08.96)	GB												
<b>(54) Title:</b> INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE  <b>(57) Abstract</b>  The present invention is directed to compounds which inhibit farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for inhibiting farnesyl-protein transferase and the farnesylation of the oncogene protein Ras.														

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

- 1 -

TITLE OF THE INVENTION

## INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

BACKGROUND OF THE INVENTION

5           The Ras proteins (Ha-Ras, Ki4a-Ras, Ki4b-Ras and N-Ras) are part of a signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP.

10   Upon growth factor receptor activation Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and

15   D.M. Willumsen, *Ann. Rev. Biochem.* 62:851-891 (1993)). Mutated *ras* genes (Ha-*ras*, Ki4a-*ras*, Ki4b-*ras* and N-*ras*) are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit

20   a growth stimulatory signal.

          Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus

25   contains a sequence motif termed a "CAAX" or "Cys-Aaa<sup>1</sup>-Aaa<sup>2</sup>-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al.*, *Nature* 310:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein

30   transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C<sub>15</sub> or C<sub>20</sub> isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem.* 61:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics* 30:209-237 (1992)). The Ras protein is one of several proteins that are known to undergo post-translational

- 2 -

farnesylation. Other farnesylated proteins include the Ras-related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem.* 269, 14182 (1994) have identified a peroxisome associated protein Pxf which  
5 is also farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Inhibition of farnesyl-protein transferase has been shown to block the growth of Ras-transformed cells in soft agar and  
10 to modify other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993) and G.L. James *et al.*, *Science*, 260:1937-1942 (1993). Recently, it has been shown  
15 that an inhibitor of farnesyl-protein transferase blocks the growth of *ras*-dependent tumors in nude mice (N.E. Kohl *et al.*, *Proc. Natl. Acad. Sci U.S.A.*, 91:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl *et al.*, *Nature Medicine*, 1:792-797 (1995).

20 Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock *et al.*, *ibid*; Casey *et al.*, *ibid*; Schafer *et al.*, *Science* 245:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including  
25 farnesyl pyrophosphate. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss *et al.*, *Cell*, 62:81-88 (1990); Schaber *et al.*, *J. Biol. Chem.*, 265:14701-14704 (1990); Schafer *et al.*, *Science*, 249:1133-1139 (1990); Manne *et al.*, *Proc. Natl. Acad. Sci USA*, 87:7541-7545 (1990)). Inhibition of farnesyl pyrophosphate  
30 biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells. However, direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side effects than would occur with the required dose of a general inhibitor

- 3 -

of isoprene biosynthesis.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in four general classes (S. Graham, *Expert Opinion Ther. Patents*, (1995) 5:1269-1285). The first are analogs of farnesyl diphosphate (FPP), while a second class of inhibitors is related to the protein substrates (e.g., Ras) for the enzyme. Bisubstrate inhibitors and inhibitors of farnesyl-protein transferase that are non-competitive with the substrates have also been described. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al.*, *ibid*; Reiss *et al.*, *ibid*; Reiss *et al.*, *PNAS*, 88:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993); Graham, *et al.*, *J. Med. Chem.*, 37, 725 (1994)). In general, deletion of the thiol from a CAAX derivative has been shown to dramatically reduce the inhibitory potency of the compound. However, the thiol group potentially places limitations on the therapeutic application of FPTase inhibitors with respect to pharmacokinetics, pharmacodynamics and toxicity. Therefore, a functional replacement for the thiol is desirable.

It has recently been disclosed that certain tricyclic compounds which optionally incorporate a piperidine moiety are inhibitors of FPTase (WO 95/10514, WO 95/10515 and WO 95/10516). Imidazole-containing inhibitors of farnesyl protein transferase have also been disclosed (WO 95/09001 and EP 0 675 112 A1).

It has recently been reported that farnesyl-protein transferase inhibitors are inhibitors of proliferation of vascular smooth muscle cells and are therefore useful in the prevention and therapy of arteriosclerosis and diabetic disturbance of blood vessels (JP H7-112930).

It is, therefore, an object of this invention to develop

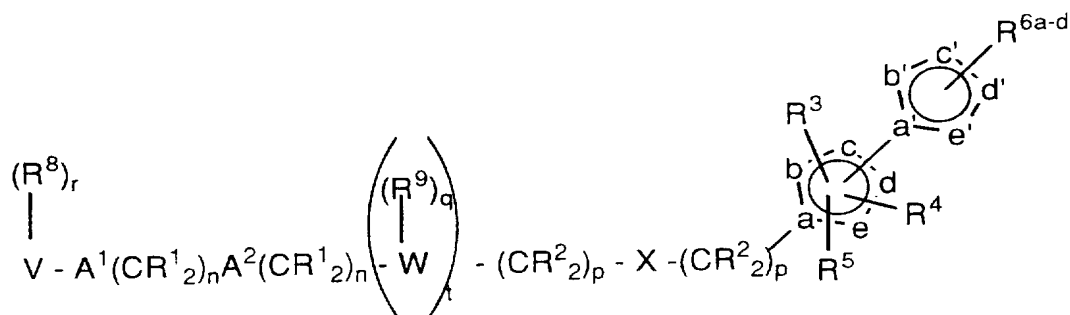
- 4 -

low molecular weight compounds that will inhibit farnesyl-protein transferase and thus, the post-translational farnesylation of proteins. It is a further object of this invention to develop chemotherapeutic compositions containing the compounds of this invention and methods for producing the compounds of this invention.

### SUMMARY OF THE INVENTION

The present invention comprises biheteroaryl-containing compounds which inhibit the farnesyl-protein transferase. Further contained in this invention are chemotherapeutic compositions containing these farnesyl transferase inhibitors and methods for their production.

The compounds of this invention are illustrated by the formula A:



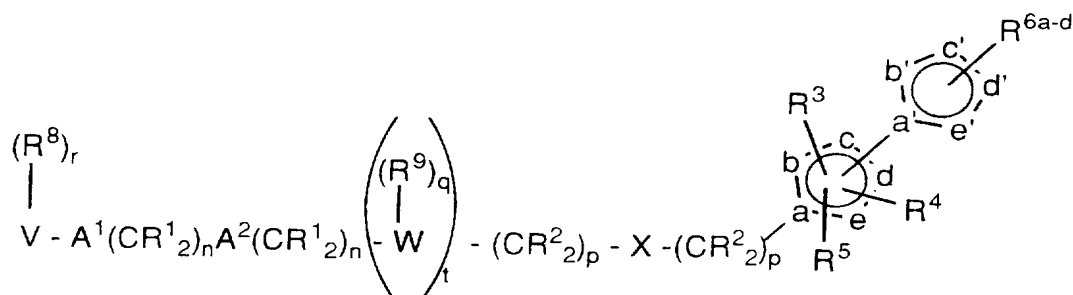
15

A

- 5 -

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. In a first embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula A:



A

wherein:

a is N or C;

10

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

15 a' is N or C;

from 0-4 of b', c', d' and e' are independently N, NH, O and S, and the remaining b', c', d' and e' atoms are independently CH, provided that if a' is C, then at least one of b', c', d' or e' is independently N, NH, O or S;

20

R<sup>1</sup> and R<sup>2</sup> are independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl,

- 6 -

C2-C6 alkynyl, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>11</sup>C(O)O-,  
 R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN,  
 NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
 5 c) unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the  
 substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from  
 unsubstituted or substituted aryl, heterocyclic,  
 C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,  
 R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-,  
 R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>,  
 10 and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently selected from:

a) hydrogen,  
 b) 15 unsubstituted or substituted aryl, unsubstituted or  
 substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub>  
 alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl,  
 R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, R<sup>11</sup>C(O)O-,  
 (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-,  
 N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
 20 c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
 d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the  
 substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or  
 substituted aryl, unsubstituted or substituted heterocyclic,  
 C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,  
 25 R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-,  
 R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and  
 R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

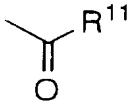
30 a) hydrogen,  
 b) unsubstituted or substituted aryl, unsubstituted or  
 substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub>  
 alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl,  
 R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, R<sup>11</sup>C(O)O-,



- 7 -

- (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

R<sup>7</sup> is selected from: H; C<sub>1</sub>-4 alkyl, C<sub>3</sub>-6 cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

- a) C<sub>1</sub>-4 alkoxy,
- b) aryl or heterocycle,
- c) halogen,
- d) HO,
- e) ,
- f) —SO<sub>2</sub>R<sup>11</sup>,
- g) N(R<sup>10</sup>)<sub>2</sub> or
- h) C<sub>1</sub>-4 perfluoroalkyl;

R<sup>8</sup> is independently selected from:

- a) hydrogen,
- b) aryl, substituted aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, perfluoroalkyl, F, Cl, Br, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and

- 8 -

- 5 c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, perfluoroalkyl, F, Cl, Br, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NH-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>10</sup>OC(O)NH-;
- provided that when R<sup>8</sup> is heterocycle, attachment of R<sup>8</sup> to V is through a substitutable ring carbon;

10 R<sup>9</sup> is independently selected from:

- a) hydrogen,
- b) C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, Br, R<sup>11</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and
- 15 c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

20 R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

25 R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl,

30 2-aminoethyl and 2,2,2-trifluoroethyl;

A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, O, -N(R<sup>10</sup>)-, -S(O)<sub>2</sub>N(R<sup>10</sup>)-, -N(R<sup>10</sup>)S(O)<sub>2</sub>-, or S(O)<sub>m</sub>;

- 9 -

V is selected from:

- a) hydrogen,
  - b) heterocycle,
  - 5 c) aryl,
  - d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
  - e) C<sub>2</sub>-C<sub>20</sub> alkenyl,
- 10 provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>; and provided that when V is heterocycle, attachment of V to R<sup>8</sup> and to A<sup>1</sup> is through a substitutable ring carbon;

15 W is a heterocycle;

X is a bond, -CH=CH-, O, -C(=O)-, -C(O)NR<sup>7</sup>-, -NR<sup>7</sup>C(O)-, -C(O)O-, -OC(O)-, -C(O)NR<sup>7</sup>C(O)-, -NR<sup>7</sup>-, -S(O)<sub>2</sub>N(R<sup>10</sup>)-, -N(R<sup>10</sup>)S(O)<sub>2</sub>- or -S(=O)<sub>m</sub>-, provided that if a is N, then

20 X is not O, -C(O)NR<sup>7</sup>-, -C(O)O-, -C(O)NR<sup>7</sup>C(O)-, -S(O)<sub>2</sub>N(R<sup>10</sup>)- or -NR<sup>7</sup>-;

m is 0, 1 or 2;

n is independently 0, 1, 2, 3 or 4;

25 p is independently 0, 1, 2, 3 or 4;

q is 0, 1, 2 or 3;

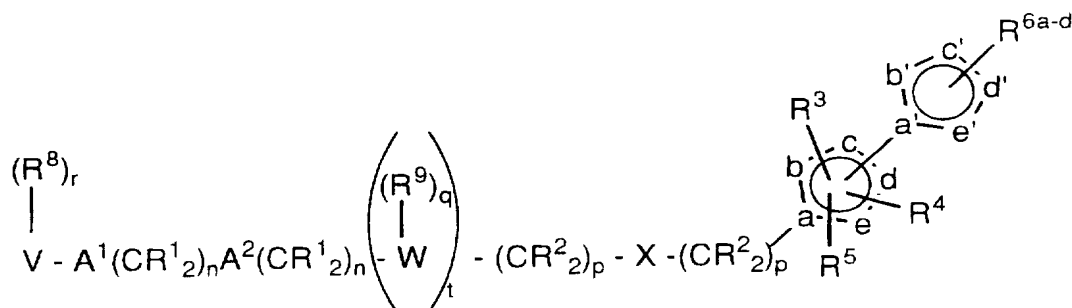
r is 0 to 5, provided that r is 0 when V is hydrogen; and

t is 0 or 1;

30 or the pharmaceutically acceptable salts thereof.

A preferred embodiment of the compounds of this invention is illustrated by the following formula A:

- 10 -



wherein:

a is N or C;

5

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH; O or S;

10 a' is N or C;

from 0-4 of b', c', d' and e' are independently N, NH, O and S, and the remaining b', c', d' and e' atoms are independently CH, provided that if a' is C, then at least one of b', c', d' or e' is independently N, NH, O or

15 S;

R<sup>1</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>1</sub>-C<sub>6</sub> alkyl;

20 R<sup>2</sup> is independently selected from:

- a) hydrogen,
  - b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>2</sub>-C<sub>6</sub> alkenyl,
  - c) unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the
- 25 substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from

- 11 -

unsubstituted or substituted aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O- and -N(R<sup>10</sup>)<sub>2</sub>;

R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently selected from:

- 5 a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- 10 c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl;
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;
- 15
- 20

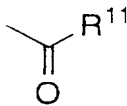
R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- 25 c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl;
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-,
- 30

- 12 -

$R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  $R^{10}_2N-C(NR^{10})-$ , CN,  
 $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , and  $R^{11}OC(O)-NR^{10}-$ ;

5  $R^7$  is selected from: H; C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, heterocycle, aryl,  
 aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or  
 substituted with:

- 10 a) C<sub>1-4</sub> alkoxy,  
 b) aryl or heterocycle,  
 c) halogen,  
 d) HO,  
 e) ,  
 f)  $-SO_2R^{11}$ ,  
 g)  $N(R^{10})_2$  or  
 h) C<sub>1-4</sub> perfluoroalkyl;

15  $R^8$  is independently selected from:

- a) hydrogen,  
 b) aryl, substituted aryl, heterocycle, C<sub>1-C6</sub> alkyl, C<sub>2-C6</sub>  
 alkenyl, C<sub>2-C6</sub> alkynyl, C<sub>1-C6</sub> perfluoroalkyl, F, Cl,  
 20  $R^{10}O-$ ,  $R^{10}C(O)NR^{10}-$ , CN, NO<sub>2</sub>,  $(R^{10})_2N-C(NR^{10})-$ ,  
 $R^{10}C(O)-$ ,  $-N(R^{10})_2$ , or  $R^{11}OC(O)NR^{10}-$ , and  
 c) C<sub>1-C6</sub> alkyl substituted by C<sub>1-C6</sub> perfluoroalkyl,  $R^{10}O-$ ,  
 $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2N-C(NR^{10})-$ ,  $R^{10}C(O)-$ ,  
 $-N(R^{10})_2$ , or  $R^{11}OC(O)NR^{10}-$ ;

25 provided that when  $R^8$  is heterocycle, attachment of  $R^8$  to V is  
 through a substitutable ring carbon;

$R^9$  is selected from:

- a) hydrogen,  
 b) C<sub>2-C6</sub> alkenyl, C<sub>2-C6</sub> alkynyl, C<sub>1-C6</sub> perfluoroalkyl, F,  
 30 Cl,  $R^{11}O-$ ,  $R^{11}S(O)_m-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,

- 13 -

CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and

- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, CN, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR<sup>10</sup>-, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;

V is selected from:

- a) hydrogen,
- b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
- c) aryl,
- d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C<sub>2</sub>-C<sub>20</sub> alkenyl, and

provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;

- 14 -

provided that when V is heterocycle, attachment of V to R<sup>8</sup> and to A<sup>1</sup> is through a substitutable ring carbon;

W is a heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, triazolyl or isoquinolinyl;

X is a bond, O, -C(=O)-, -CH=CH-, -C(O)NR<sup>7</sup>-, -NR<sup>7</sup>C(O)-, -NR<sup>7</sup>-, -S(O)<sub>2</sub>N(R<sup>10</sup>)-, -N(R<sup>10</sup>)S(O)<sub>2</sub>- or -S(=O)<sub>m</sub>-; provided that if a is N, then X is not O, -C(O)NR<sup>7</sup>-, -S(O)<sub>2</sub>N(R<sup>10</sup>)- or -NR<sup>7</sup>-;

m is 0, 1 or 2;

n is independently 0, 1, 2, 3 or 4;

p is independently 0, 1, 2, 3 or 4;

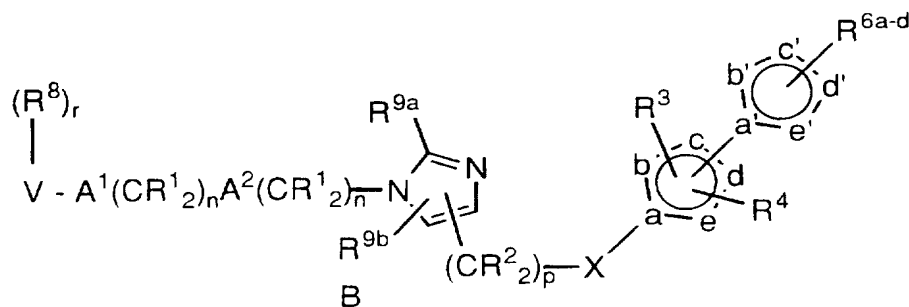
q is 0, 1, 2 or 3;

r is 0 to 5, provided that r is 0 when V is hydrogen; and

t is 0 or 1;

or the pharmaceutically acceptable salts thereof.

A preferred embodiment of the compounds of this invention are illustrated by the formula B:



wherein:

a is N or C;



- 15 -

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

5 a' is N or C:

from 0-4 of b', c', d' and e' are independently N, NH, O and S, and the remaining b', c', d' and e' atoms are independently CH, provided that if a' is C, then at least one of b', c', d' or e' is independently N, NH, O or S;

10 S;

R<sup>1</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>1</sub>-C<sub>6</sub> alkyl;

15 R<sup>2</sup> is independently selected from:

- a) hydrogen,
  - b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>2</sub>-C<sub>6</sub> alkenyl,
  - c) unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O- and -N(R<sup>10</sup>)<sub>2</sub>;
- 20

R<sup>3</sup> and R<sup>4</sup> are independently selected from:

- a) hydrogen,
  - b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
  - c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
  - d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or
- 25
- 30

- 16 -

5 substituted aryl, unsubstituted or substituted heterocyclic, C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

- 10 a) hydrogen,  
 b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl, halogen, C1-C6 perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
 15 c) unsubstituted C1-C6 alkyl,  
 d) substituted C1-C6 alkyl wherein the substituent on the substituted C1-C6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;
- 20

R<sup>8</sup> is independently selected from:

- 25 a) hydrogen,  
 b) aryl, substituted aryl, heterocycle, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and  
 30 c) C1-C6 alkyl substituted by C1-C6 perfluoroalkyl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

provided that when R<sup>8</sup> is heterocycle, attachment of R<sup>8</sup> to V is through a substitutable ring carbon;

- 17 -

R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, trifluoromethyl and halogen;

- 5 R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

- 10 R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

15

A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR<sup>10</sup>-, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;

V is selected from:

- 20 a) hydrogen,  
b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,  
c) aryl,  
25 d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and  
e) C<sub>2</sub>-C<sub>20</sub> alkenyl, and

30 provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;

provided that when V is heterocycle, attachment of V to R<sup>8</sup> and to A<sup>1</sup> is through a substitutable ring carbon;

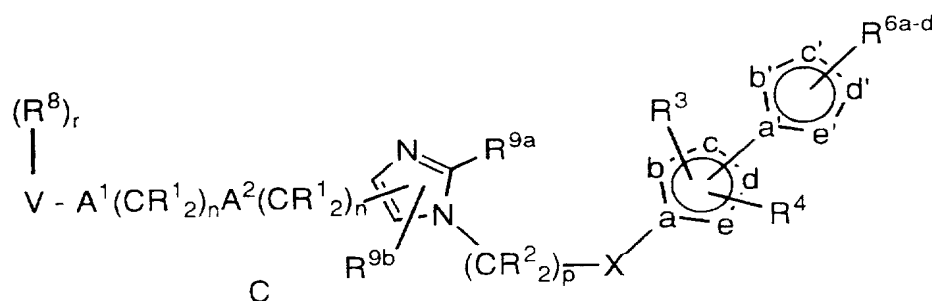
- 18 -

X is a bond, -CH=CH-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, -NR<sup>10</sup>-, O or -C(=O)-;  
provided that if a is N, then X is not -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>-, or O;

- 5    m is            0, 1 or 2;  
     n is            0, 1, 2, 3 or 4;  
     p is            0, 1, 2, 3 or 4; and  
     r is            0 to 5, provided that r is 0 when V is hydrogen;

10   or the pharmaceutically acceptable salts thereof.

Another preferred embodiment of the compounds of this invention are illustrated by the formula C:



wherein:

15

a is N or C;

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a

20

is C, then at least one of b, c, d or e is independently N, NH, O or S;

a' is N or C;

25

from 0-4 of b', c', d' and e' are independently N, NH, O and S, and the remaining b', c', d' and e' atoms are independently CH, provided that if a' is C, then at least one of b', c', d' or e' is independently N, NH, O or S;

- 19 -

R<sup>1</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>1</sub>-C<sub>6</sub> alkyl;

5 R<sup>2</sup> is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>2</sub>-C<sub>6</sub> alkenyl,
- c) unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the  
10 substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O- and -N(R<sup>10</sup>)<sub>2</sub>;

R<sup>3</sup> and R<sup>4</sup> are independently selected from:

- 15 a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN(R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- 20 c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or  
25 substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;
- 30

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub>

- 20 -

- alkenyl, C2-C6 alkynyl, halogen, C1-C6 perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN(R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- 5 c) unsubstituted C1-C6 alkyl,
- d) substituted C1-C6 alkyl wherein the substituent on the substituted C1-C6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl,
- 10 R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

R<sup>8</sup> is independently selected from:

- 15 a) hydrogen,
- b) aryl, substituted aryl, heterocycle, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and
- 20 c) C1-C6 alkyl substituted by C1-C6 perfluoroalkyl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

provided that when R<sup>8</sup> is heterocycle, attachment of R<sup>8</sup> to V is through a substitutable ring carbon;

25 R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, C1-C6 alkyl, trifluoromethyl and halogen;

30 R<sup>10</sup> is independently selected from hydrogen, C1-C6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R<sup>11</sup> is independently selected from C1-C6 alkyl and aryl;

- 21 -

R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR<sup>10</sup>-, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;

10 V is selected from:

- a) hydrogen,
- b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
- 15 c) aryl,
- d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C<sub>2</sub>-C<sub>20</sub> alkenyl, and

20 provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;  
provided that when V is heterocycle, attachment of V to R<sup>8</sup> and to A<sup>1</sup> is through a substitutable ring carbon;

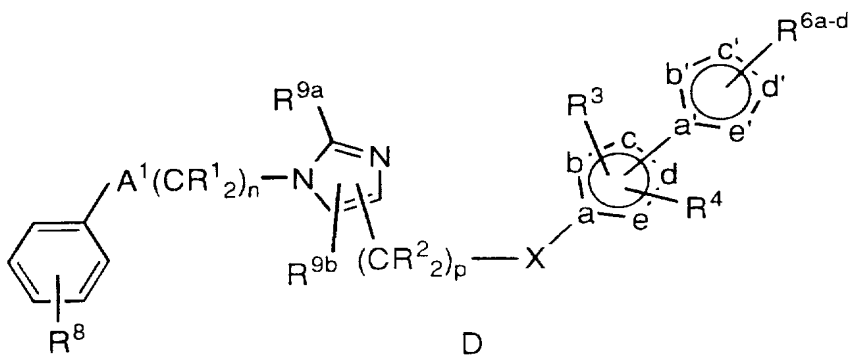
25 X is a bond, -CH=CH-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, -NR<sup>10</sup>-, O or -C(=O)-;  
provided that if a is N, then X is not -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>- or O;

m is 0, 1 or 2;  
30 n is 0, 1, 2, 3 or 4;  
p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond, -NR<sup>10</sup>- or O; and  
r is 0 to 5, provided that r is 0 when V is hydrogen;

- 22 -

or the pharmaceutically acceptable salts thereof.

In a more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula D:



wherein:

a is N or C;

- 10 from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

a' is N or C;

- 15 from 0-4 of b', c', d' and e' are independently N, NH, O and S, and the remaining b', c', d' and e' atoms are independently CH, provided that if a' is C, then at least one of b', c', d' or e' is independently N, NH, O or S;

- 20 R<sup>1</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup> is independently selected from:

- 25 a) hydrogen,  
b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>,



- 23 -

F or C<sub>2</sub>-C<sub>6</sub> alkenyl,

- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O-, or -N(R<sup>10</sup>)<sub>2</sub>;

5

R<sup>3</sup> is selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

10

15

20

R<sup>4</sup> is selected from H, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl and CF<sub>3</sub>;25 R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,

30

- 24 -

- 5 d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

R<sup>8</sup> is independently selected from:

- 10 a) hydrogen,  
 b) aryl, substituted aryl, heterocycle, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and  
 15 c) C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

provided that when R<sup>8</sup> is heterocycle, attachment of R<sup>8</sup> to V is through a substitutable ring carbon;

20 R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, halogen, CF<sub>3</sub> or methyl;

R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

25 R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A<sup>1</sup> is selected from: a bond, -C(O)-, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;

- 25 -

X is a bond,  $-\text{CH}=\text{CH}-$ ,  $-\text{C}(\text{O})\text{NR}^{10}-$ ,  $-\text{NR}^{10}\text{C}(\text{O})-$ ,  $-\text{NR}^{10}-$ , O or  $-\text{C}(=\text{O})-$ , provided that if a is N, then X is not  $-\text{C}(\text{O})\text{NR}^{10}-$ ,  $-\text{NR}^{10}-$  or O;

5

n is 0 or 1; provided that n is not 0 if  $\text{A}^1$  is a bond, O,  $-\text{N}(\text{R}^{10})-$ , or  $\text{S}(\text{O})_m$ ;

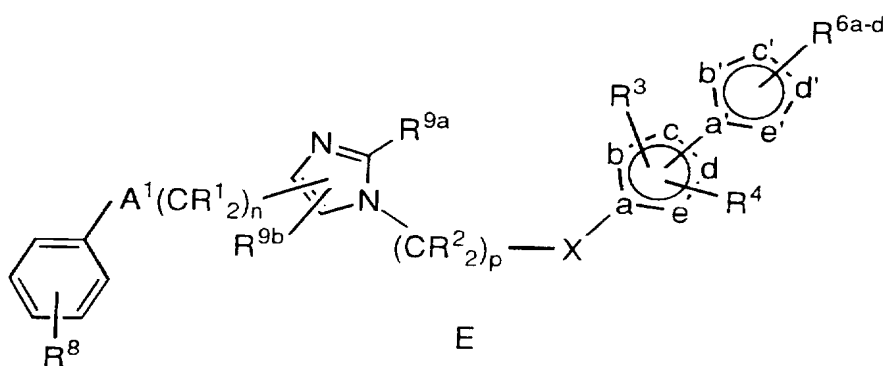
m is 0, 1 or 2; and

p is 0, 1, 2, 3 or 4;

10

or the pharmaceutically acceptable salts thereof.

In another more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula E:



15

wherein:

a is N or C;

20 from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

a' is N or C;

25

- 26 -

from 0-4 of b', c', d' and e' are independently N, NH, O and S, and the remaining b', c', d' and e' atoms are independently CH, provided that if a' is C, then at least one of b', c', d' or e' is independently N, NH, O or S;

5

R<sup>1</sup> is independently selected from: hydrogen, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F, C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup> is independently selected from:

10

- a) hydrogen,
- b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>2</sub>-C<sub>6</sub> alkenyl,
- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O-, or -N(R<sup>10</sup>)<sub>2</sub>;

15

R<sup>3</sup> is selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

20

25

30

R<sup>4</sup> is selected from H, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl and CF<sub>3</sub>;

- 27 -

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

R<sup>8</sup> is independently selected from:

- a) hydrogen,
- b) aryl, substituted aryl, heterocycle, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and
- c) C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

provided that when R<sup>8</sup> is heterocycle, attachment of R<sup>8</sup> to V is through a substitutable ring carbon;

R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, halogen, CF<sub>3</sub> or methyl;

R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

- 28 -

$R^{11}$  is independently selected from  $C_1$ - $C_6$  alkyl and aryl;

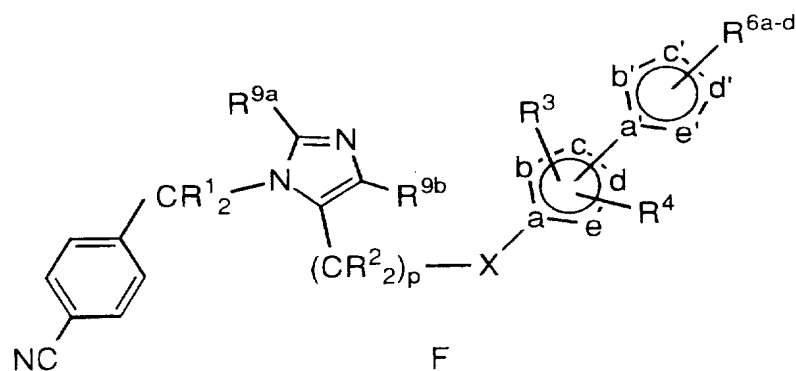
5  $R^{12}$  is independently selected from hydrogen,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  aralkyl,  $C_1$ - $C_6$  substituted aralkyl,  $C_1$ - $C_6$  heteroaralkyl,  $C_1$ - $C_6$  substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,  $C_1$ - $C_6$  perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

10 X is a bond,  $-\text{CH}=\text{CH}-$ ,  $-\text{C}(\text{O})\text{NR}^{10}-$ ,  $-\text{NR}^{10}\text{C}(\text{O})-$ ,  $-\text{NR}^{10}-$ , O or  $-\text{C}(=\text{O})-$ ;  
provided that if a is N, then X is not  $-\text{C}(\text{O})\text{NR}^{10}-$ ,  $-\text{NR}^{10}-$  or O;

n is 0 or 1;  
15 m is 0, 1 or 2; and  
p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond,  $-\text{NR}^{10}-$  or O;

or the pharmaceutically acceptable salts thereof.

20 In a further embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula F:



wherein:

25 a is N or C;

- 29 -

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

5 a' is N or C;

from 0-4 of b', c', d' and e' are independently N, NH, O and S, and the remaining b', c', d' and e' atoms are independently CH, provided that if a' is C, then at least one of b', c', d' or e' is independently N, NH, O or S;

10 S;

R<sup>1</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

15 R<sup>2</sup> is independently selected from:

- a) hydrogen,
  - b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub> or F,
  - c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl,
- 20 heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, or -N(R<sup>10</sup>)<sub>2</sub>;

R<sup>3</sup> is selected from:

- a) hydrogen,
  - b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- 25
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
  - d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,
- 30

- 30 -

$R^{12}O-$ ,  $R^{11}S(O)_m-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  
 $R^{10}_2N-C(NR^{10})-$ ,  $CN$ ,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , and  
 $R^{11}OC(O)-NR^{10}-$ ;

5  $R^4$  is selected from H, halogen,  $CH_3$  and  $CF_3$ ;

$R^{6a}$ ,  $R^{6b}$ ,  $R^{6c}$  and  $R^{6d}$  are independently selected from:

- a) hydrogen,
- b) 10 unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,  $C_3-C_{10}$  cycloalkyl,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl, halogen,  $C_1-C_6$  perfluoroalkyl,  $R^{12}O-$ ,  $R^{11}S(O)_m-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  $R^{10}_2N-C(NR^{10})-$ ,  $CN$ ,  $NO_2$ ,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , or  $R^{11}OC(O)NR^{10}-$ ,
- c) 15 unsubstituted  $C_1-C_6$  alkyl,
- d) substituted  $C_1-C_6$  alkyl wherein the substituent on the substituted  $C_1-C_6$  alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic,  $C_3-C_{10}$  cycloalkyl,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl, 20  $R^{12}O-$ ,  $R^{11}S(O)_m-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  $R^{10}_2N-C(NR^{10})-$ ,  $CN$ ,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , and  $R^{11}OC(O)-NR^{10}-$ ;

25  $R^{9a}$  and  $R^{9b}$  are independently hydrogen, halogen,  $CF_3$  or methyl;

$R^{10}$  is independently selected from hydrogen,  $C_1-C_6$  alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

30  $R^{11}$  is independently selected from  $C_1-C_6$  alkyl and aryl;

$R^{12}$  is independently selected from hydrogen,  $C_1-C_6$  alkyl,  $C_1-C_6$  aralkyl,  $C_1-C_6$  substituted aralkyl,  $C_1-C_6$  heteroaralkyl,  $C_1-C_6$  substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,  $C_1-C_6$  perfluoroalkyl,



- 31 -

2-aminoethyl and 2,2,2-trifluoroethyl;

X is a bond, -CH=CH-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, -NR<sup>10</sup>-, O or -C(=O)-;

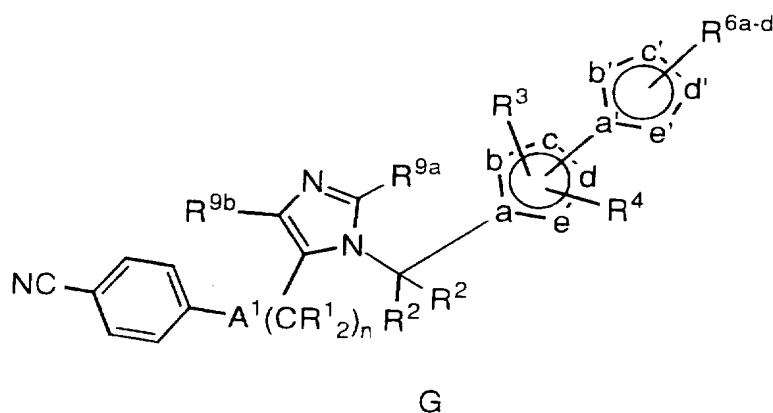
5 provided that if a is N, then X is not -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>- or O;

m is 0, 1 or 2; and

p is 0, 1, 2, 3 or 4;

10 or the pharmaceutically acceptable salts thereof.

In a further embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula G:



wherein:

15

a is C;

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a

20 is C, then at least one of b, c, d or e is independently N, NH, O or S;

a' is N or C;

from 0-4 of b', c', d' and e' are independently N, NH, O and S, and the

25 remaining b', c', d' and e' atoms are independently CH, provided that if

- 32 -

a' is C, then at least one of b', c', d' or e' is independently N, NH, O or S;

5 R<sup>1</sup> is independently selected from: hydrogen, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F, C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup> is independently selected from:

- 10 a) hydrogen,  
b) aryl, heterocycle or C<sub>3</sub>-C<sub>10</sub> cycloalkyl,  
c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O-, or -N(R<sup>10</sup>)<sub>2</sub>;

R<sup>3</sup> is selected from:

- 15 a) hydrogen,  
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
20 c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;  
25

30 R<sup>4</sup> is selected from H, halogen, CH<sub>3</sub> and CF<sub>3</sub>;

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

- a) hydrogen,

- 33 -

- 5           b)    unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- 10           c)    unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d)    substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;
- 15
- R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, halogen, CF<sub>3</sub> or methyl;
- 20   R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;
- R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;
- 25   R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;
- 30   A<sup>1</sup> is selected from: a bond, -C(O)-, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;
- m is           0, 1 or 2; and
- n is           0 or 1;

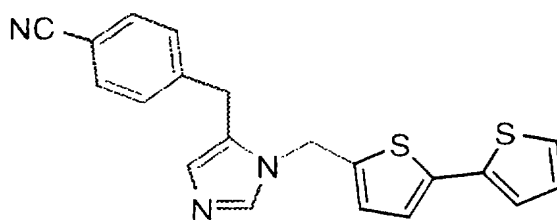
- 34 -

or the pharmaceutically acceptable salts thereof.

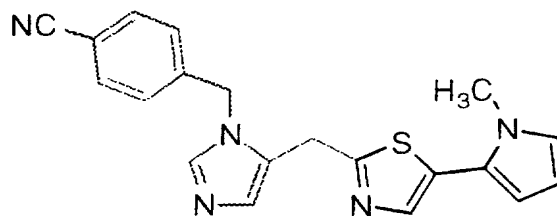
Specific examples of the compounds of the invention are:

1-(5-(Thien-2'-yl)thien-2-ylmethyl)-5-(4-cyanobenzyl)imidazole

5



1-(4-Cyanobenzyl)-5-(5-(1-methylpyrrol-2-yl)-thiazol-2-ylmethyl)imidazole



10 or the pharmaceutically acceptable salts thereof.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" and the alkyl portion of aralkyl and similar terms, is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

20

As used herein, "cycloalkyl" is intended to include non-aromatic cyclic hydrocarbon groups having the specified number of

- 35 -

carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

"Alkenyl" groups include those groups having the specified number of carbon atoms and having one or several double bonds.

- 5 Examples of alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, isoprenyl, farnesyl, geranyl, geranylgeranyl and the like.

- 10 "Alkynyl" groups include those groups having the specified number of carbon atoms and having one triple bonds. Examples of alkynyl groups include acetylene, 2-butyne, 2-pentyne, 3-pentyne and the like.

"Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

- 15 As used herein, "aryl," and the aryl portion of aralkyl, is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or  
20 acenaphthyl.

- The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to  
25 four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements  
30 include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothioapyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothioapyranyl, dihydrobenzothioapyranyl sulfone, furyl, imidazolidinyl, imidazolinyl,

- 36 -

imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopyrrolidinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl.

As used herein, "heteroaryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples of such heterocyclic elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, triazolyl and thienyl.

As used herein in the definition of R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6a-d</sup>, the term "the substituted group" is intended to mean a substituted C<sub>1-8</sub> alkyl, substituted C<sub>2-8</sub> alkenyl, substituted C<sub>2-8</sub> alkynyl, substituted aryl or substituted heterocycle from which the substituent(s) R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6a-e</sup> are selected.

As used herein in the definition of R<sup>7</sup>, the substituted C<sub>1-8</sub> alkyl, substituted C<sub>3-6</sub> cycloalkyl, substituted aroyl, substituted aryl, substituted heteroaroyl, substituted arylsulfonyl, substituted heteroaryl-sulfonyl and substituted heterocycle include moieties containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound.

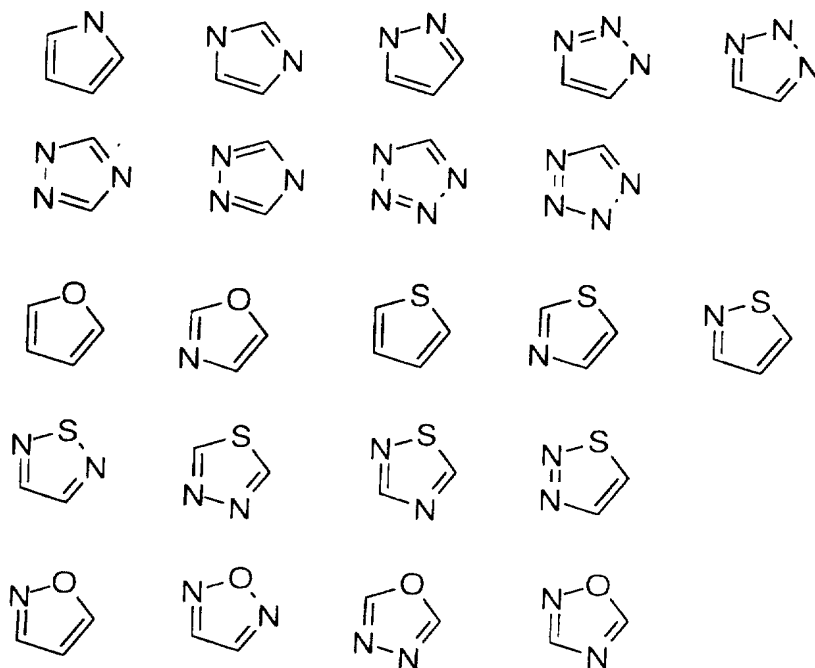
- 37 -

As used herein, when no specific substituents are set forth, the terms "substituted aryl", "substituted heterocycle" and "substituted cycloalkyl" are intended to include the cyclic group which is substituted on a substitutable ring carbon atom with 1 or 2 substituents selected from the group which includes but is not limited to F, Cl, Br, CF<sub>3</sub>, NH<sub>2</sub>, N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, NO<sub>2</sub>, CN, (C<sub>1</sub>-C<sub>6</sub> alkyl)O-, -OH, (C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>m</sub>-, (C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)NH-, H<sub>2</sub>N-C(NH)-, (C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)-, (C<sub>1</sub>-C<sub>6</sub> alkyl)OC(O)-, N<sub>3</sub>, (C<sub>1</sub>-C<sub>6</sub> alkyl)OC(O)NH-, phenyl, pyridyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furyl, isothiazolyl and C<sub>1</sub>-C<sub>20</sub> alkyl.

The moieties designated by the following structures

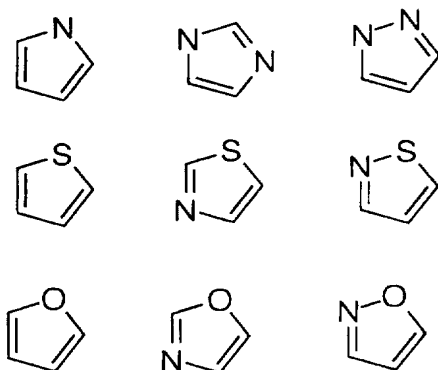


represent aromatic 5-membered heterocyclic rings and includes the following ring systems:

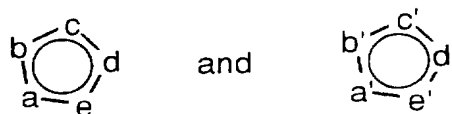


Preferably the aromatic 5-membered heterocyclic ring is selected from:

- 38 -



It is understood that such ring systems may be independently selected and that



5 may be the same or different in the instant compounds.

Lines drawn into the ring systems from substituents (such as from  $R^3$ ,  $R^4$  etc.) means that the indicated bond may be attached to any of the substitutable ring carbon or nitrogen atoms.

10 Preferably,  $R^1$  and  $R^2$  are independently selected from: hydrogen,  $R^{11}C(O)O-$ ,  $-N(R^{10})_2$ ,  $R^{10}C(O)NR^{10}-$ ,  $R^{10}O-$  or unsubstituted or substituted  $C_1-C_6$  alkyl wherein the substituent on the substituted  $C_1-C_6$  alkyl is selected from unsubstituted or substituted phenyl,  $-N(R^{10})_2$ ,  $R^{10}O-$  and  $R^{10}C(O)NR^{10}-$ .

Preferably,  $R^3$  is selected from:

- 15 a) hydrogen,  
 b)  $C_3-C_{10}$  cycloalkyl, halogen,  $C_1-C_6$  perfluoroalkyl,  $R^{12}O-$ , CN,  $NO_2$ ,  $R^{10}C(O)-$  or  $-N(R^{10})_2$ ,  
 c) unsubstituted  $C_1-C_6$  alkyl,  
 d) substituted  $C_1-C_6$  alkyl wherein the substituent on the  
 20 substituted  $C_1-C_6$  alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic,  $C_3-C_{10}$  cycloalkyl,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl,



- 39 -

$R^{12}O-$ ,  $R^{11}S(O)_m-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  
 $R^{10}_2N-C(NR^{10})-$ , CN,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , and  
 $R^{11}OC(O)-NR^{10}-$ .

5 Preferably,  $R^4$  is selected from: hydrogen, halogen,  
 trifluoromethyl, trifluoromethoxy and  $C_1$ - $C_6$  alkyl.

Preferably,  $R^5$  is hydrogen.

Preferably,  $R^{6a}$ ,  $R^{6b}$ ,  $R^{6c}$  and  $R^{6d}$  are independently  
 selected from:

- a) hydrogen,
- 10 b)  $C_3$ - $C_{10}$  cycloalkyl, halogen,  $C_1$ - $C_6$  perfluoroalkyl,  $R^{12}O-$ ,  
 $R^{11}S(O)_m-$ , CN,  $NO_2$ ,  $R^{10}C(O)-$  or  $-N(R^{10})_2$ ,
- c) unsubstituted  $C_1$ - $C_6$  alkyl;
- d) substituted  $C_1$ - $C_6$  alkyl wherein the substituent on the  
 15 substituted  $C_1$ - $C_6$  alkyl is selected from unsubstituted or  
 substituted aryl,  $C_3$ - $C_{10}$  cycloalkyl,  $R^{12}O-$ ,  $R^{11}S(O)_m-$ ,  
 $R^{10}C(O)-$  or  $-N(R^{10})_2$ .

Preferably,  $R^8$  is independently selected from:

- a) hydrogen, and
- 20 b) aryl, substituted aryl, heterocycle, substituted heterocycle,  
 $C_1$ - $C_6$  perfluoroalkyl or CN.

Preferably,  $R^9$  is hydrogen, halogen,  $CF_3$  or methyl.

Preferably,  $R^{10}$  is selected from H,  $C_1$ - $C_6$  alkyl and  
 benzyl.

25 Preferably,  $A^1$  and  $A^2$  are independently selected from:  
 a bond,  $-C(O)NR^{10}-$ ,  $-NR^{10}C(O)-$ , O,  $-N(R^{10})-$ ,  $-S(O)_2N(R^{10})-$  and  
 $-N(R^{10})S(O)_2-$ .

Preferably, V is selected from hydrogen, heterocycle and  
 aryl. More preferably, V is phenyl.

30 Preferably, W is selected from imidazolyl, imidazolyl,  
 oxazolyl, pyrazolyl, pyrrolidinyl, thiazolyl and pyridyl. More  
 preferably, W is selected from imidazolyl and pyridyl.

Preferably, n and r are independently 0, 1, or 2.

Preferably s is 0.

Preferably t is 1.

- 40 -

It is intended that the definition of any substituent or variable (e.g., R<sup>1</sup>, R<sup>2</sup>, R<sup>9</sup>, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, -N(R<sup>10</sup>)<sub>2</sub> represents -NHH, -NHCH<sub>3</sub>, -NHC<sub>2</sub>H<sub>5</sub>, etc. It is understood  
5 that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

10 The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic,  
15 sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic,  
20 isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared either by ion exchange  
25 chroma-tography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the Schemes 1-24,  
30 in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R<sup>3</sup>, R<sup>6</sup> and R<sup>8</sup>, as shown in the Schemes, represent the substituents R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup>, R<sup>6d</sup> and R<sup>8</sup>; although only one such R<sup>6</sup> or R<sup>8</sup> is present

- 41 -

in the intermediates and products of the schemes, it is understood that the reactions shown are also applicable when such aryl or heteroaryl moieties contain multiple substituents.

5        These reactions may be employed in a linear sequence  
to provide the compounds of the invention or they may be used to  
synthesize fragments which are subsequently joined by the alkylation  
reactions described in the Schemes. Other reactions useful in the  
preparation of heteroaryl moieties are described in "Comprehensive  
Organic Chemistry, Volume 4: Heterocyclic Compounds" ed. P.G.  
10    Sammes, Oxford (1979) and references therein. Aryl-aryl coupling  
is generally described in "Comprehensive Organic Functional Group  
Transformations," Katritzky et al. eds., pp 472-473, Pergamon Press  
(1995).

15    Synopsis of Schemes 1-24:

The requisite intermediates are in some cases commercially  
available, or can be prepared according to literature procedures, for the  
most part. Schemes 1- 14 illustrate synthesis of the instant diheteroaryl  
compound which incorporate a preferred benzylimidazolyl sidechain.

20    Thus, in Scheme 1, for example, the commercially available dithienyl-  
carboxylic acid I may be reduced. The triflate of the intermediate  
alcohol II may be formed in situ and coupled to a suitably substituted  
benzylimidazolyl III to provide, after deprotection, the instant  
compound IV.

25        Those biheteroaryl intermediates that are not commercially  
available may be synthesized by methods known in the art as well as  
those reactions illustrated in Schemes 2-6. Thus, as illustrated in  
Scheme 2 a thienyl boronic acid V may be reacted under Suzuki  
coupling conditions (*Pure Appl. Chem.*, 63:419 (1991)) with a suitably  
30    substituted halogenated heteroaryl moiety, such as 2-bromo, to provide  
the biheteroaryl carboxylic acid VI, which can then be processed as  
described in Scheme 1. Scheme 3 illustrates the analogous series of  
reactions starting with the halogenated heteroarylaldehyde.

- 42 -

Scheme 4 illustrates the reaction wherein the "terminal" heteroaryl moiety is employed in the Suzuki coupling as the halogenated reactant. Such a coupling reaction is also compatible when one of the reactants incorporates a suitably protected hydroxyl functionality as illustrated in Scheme 5.

Negishi chemistry (*Org. Synth.*, 66:67 (1988)) may also be employed to form the biheteroaryl component of the instant compounds, as shown in Scheme 6. Thus, a zinc bromide adduct, such as 3-thienyl zinc bromide, may be coupled to a suitably substituted heteroaryl halide in the presence of nickel (II) to provide the biheteroaryl VII. The heteroaryl halide and the zinc bromide adduct may be selected based on the availability of the starting reagents.

As illustrated in Scheme 7, the sequence of coupling reactions may be modified such that the heteroaryl-heteroaryl bond is formed last. Thus, a suitably substituted imidazole may first be alkylated with a heteroarylmethyl halide to provide intermediate VIII. Intermediate VIII can then undergo Suzuki type coupling to a suitably substituted heteroaryl boronic acid.

Scheme 8 illustrates the synthesis of a thiazole containing instant compound from the acyclic precursors. Similar strategies may be utilized to prepare other bisheteroatom moieties.

Scheme 9 illustrates synthesis of an instant compound wherein a non-hydrogen R<sup>9b</sup> is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole IX may be selectively iodinated to provide the 5-iodoimidazole X. That imidazole may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate XI. Intermediate XI can then undergo the alkylation reactions that were described hereinabove.

Scheme 10 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the biheteroaryl via an alkyl amino, sulfonamide or amide linker. Thus, the 4-aminoalkylimidazole XII, wherein the primary amine is protected as the phthalimide, is selectively alkylated then deprotected to provide the amine XIII. The amine XIII may then react under conditions well

- 43 -

known in the art with various activated biheteroaryl moieties to provide the instant compounds shown.

Compounds of the instant invention wherein the  $A^1(CR^1_2)_nA^2(CR^1_2)_n$  linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 11. The suitably substituted phenol XIV may be reacted with methyl N-(cyano)methanimidate to provide the 4-phenoxyimidazole XV. After selective protection of one of the imidazolyl nitrogens, the intermediate XVI can undergo alkylation reactions as described for the benzylimidazoles hereinabove.

Scheme 12 illustrates an analogous series of reactions wherein the  $(CR^2_2)_pX(CR^2_2)_p$  linker of the instant compounds is oxygen. Thus, a suitably substituted haloheteroaryl alcohol, such as, is reacted with methyl N-(cyano)methanimidate to provide intermediate XVI. Intermediate XVI is then protected and, if desired to form a compound of a preferred embodiment, alkylated with a suitably protected benzyl. The intermediate XVII can then be coupled to a second heteroaryl moiety by Suzuki chemistry to provide the instant compound.

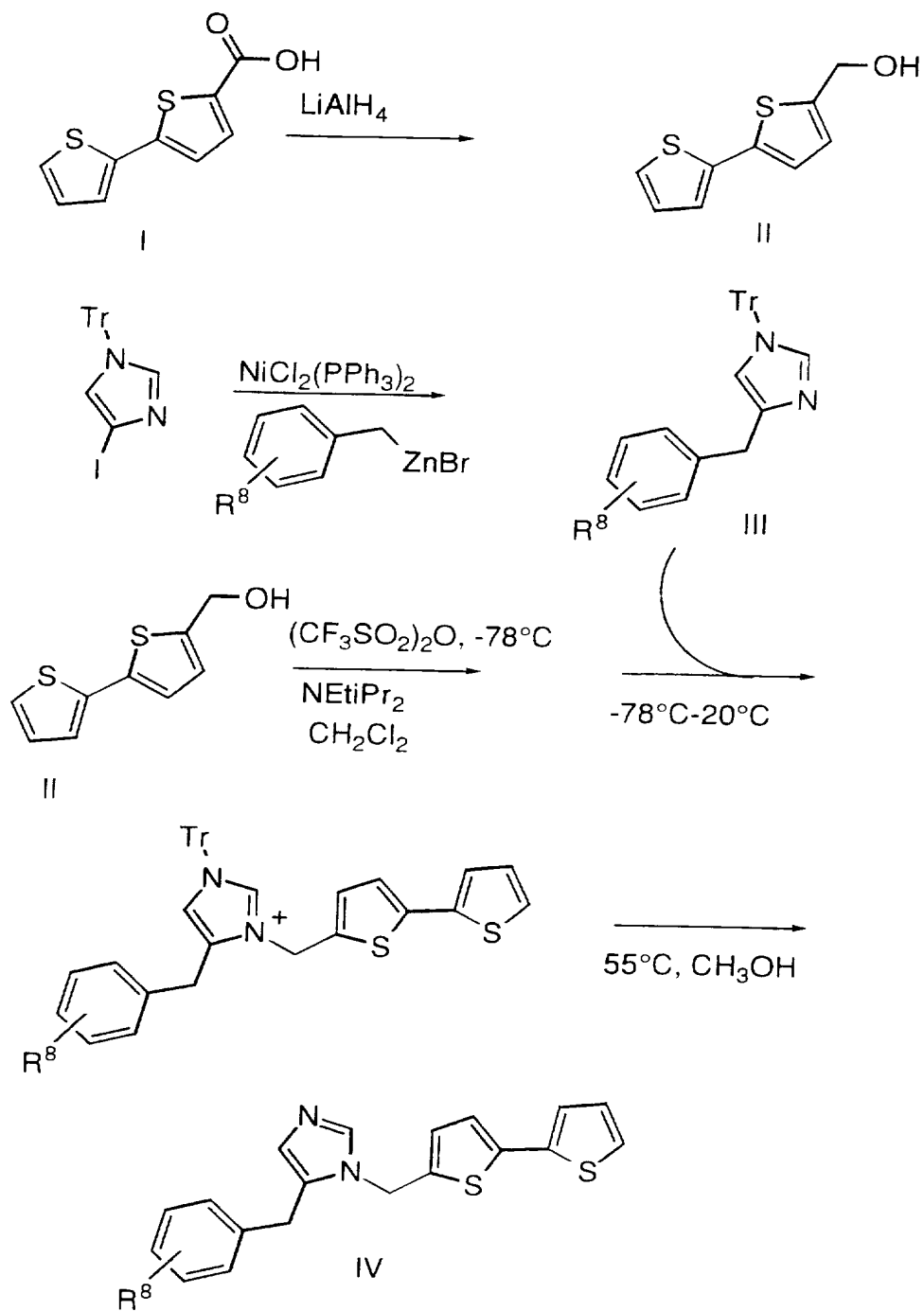
Compounds of the instant invention wherein the  $A^1(CR^1_2)_nA^2(CR^1_2)_n$  linker is a substituted methylene may be synthesized by the methods shown in Scheme 13. Thus, the N-protected imidazolyl iodide XVIII is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol XIX. Acylation, followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 1) provides the instant compound XX. If other  $R^1$  substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

Addition of various nucleophiles to an imidazolyl aldehyde may also be employed to form a substituted alkyl linker between the biheteroaryl moiety and the preferred W (imidazolyl) as shown in Scheme 14. Thus a bishalogenated five membered heteroaryl, such as 2,4-dibromothiophene, may undergo metal halogen exchange followed by reaction with a suitably substituted imidazolyl aldehyde and

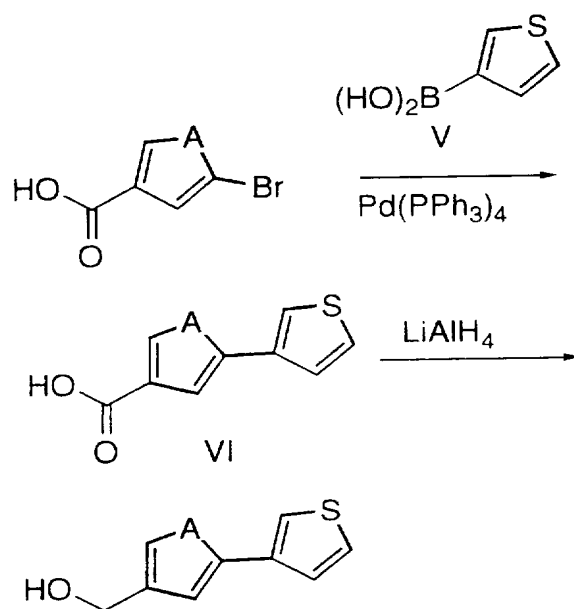
- 44 -

- 5     acetylation to form a regioisomeric mixture of the acetyl intermediates. The halogenated regioisomeric mixture may be chromatographically separated at this stage, if convenient. Suzuki coupling with a suitably substituted 5-membered heteroaryl boronic acid affords the instant acetoxy compound, which can be treated with lithium hydroxide to remove the acetyl group. Then, similar substituent manipulation as shown in Scheme 13 may be performed on a fully functionalized compound which incorporates an R<sup>2</sup> hydroxyl moiety.

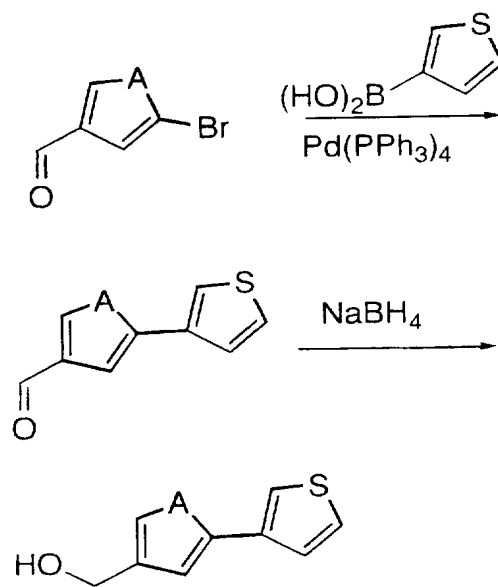
- 45 -

SCHEME 1

- 46 -

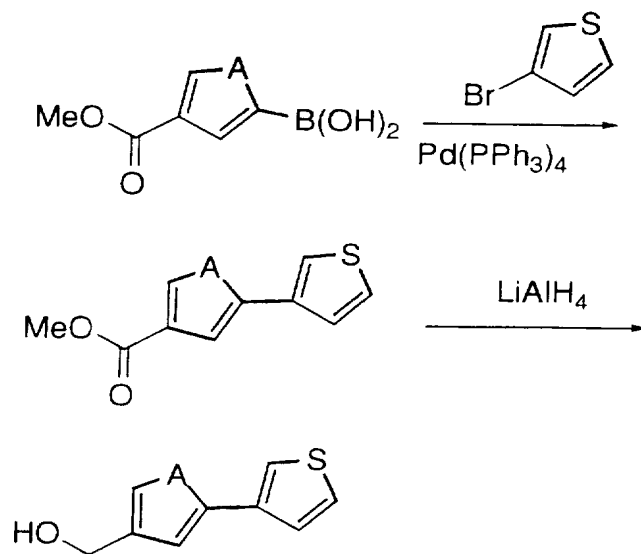
SCHEME 2

5

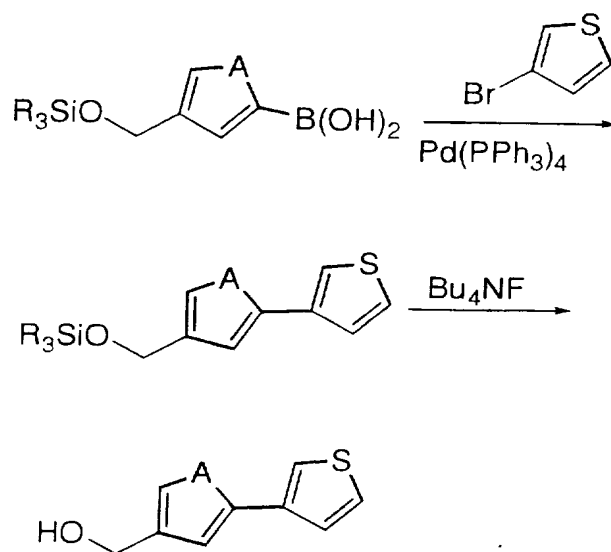
SCHEME 3



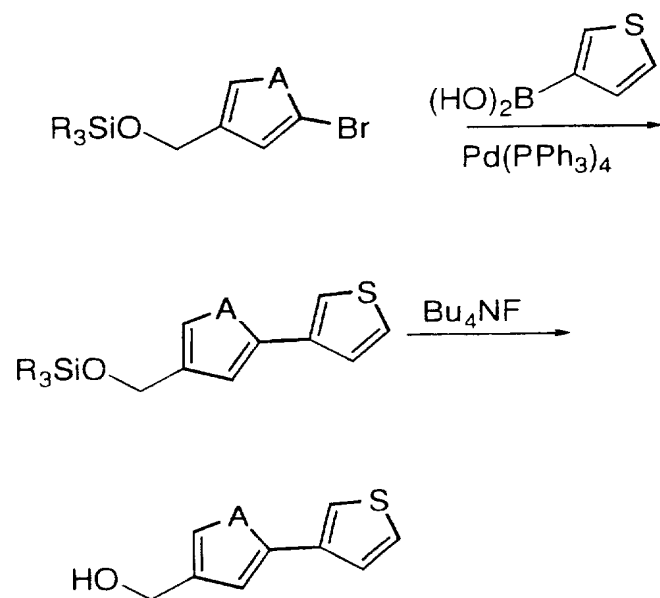
- 47 -

SCHEME 4

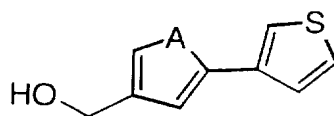
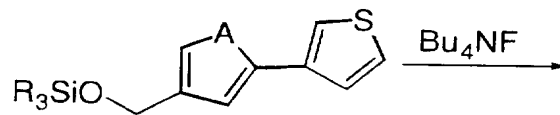
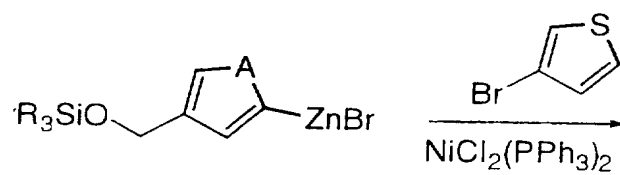
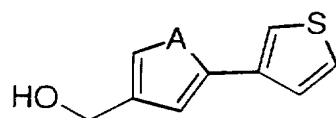
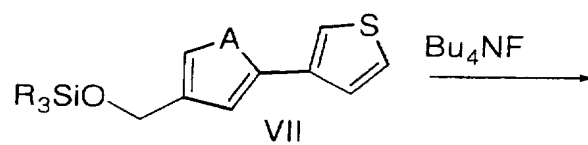
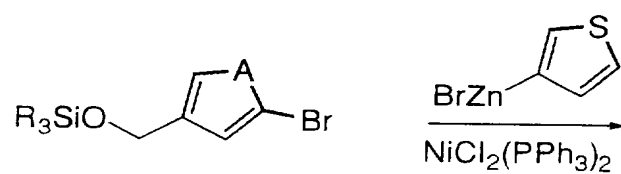
5

SCHEME 5

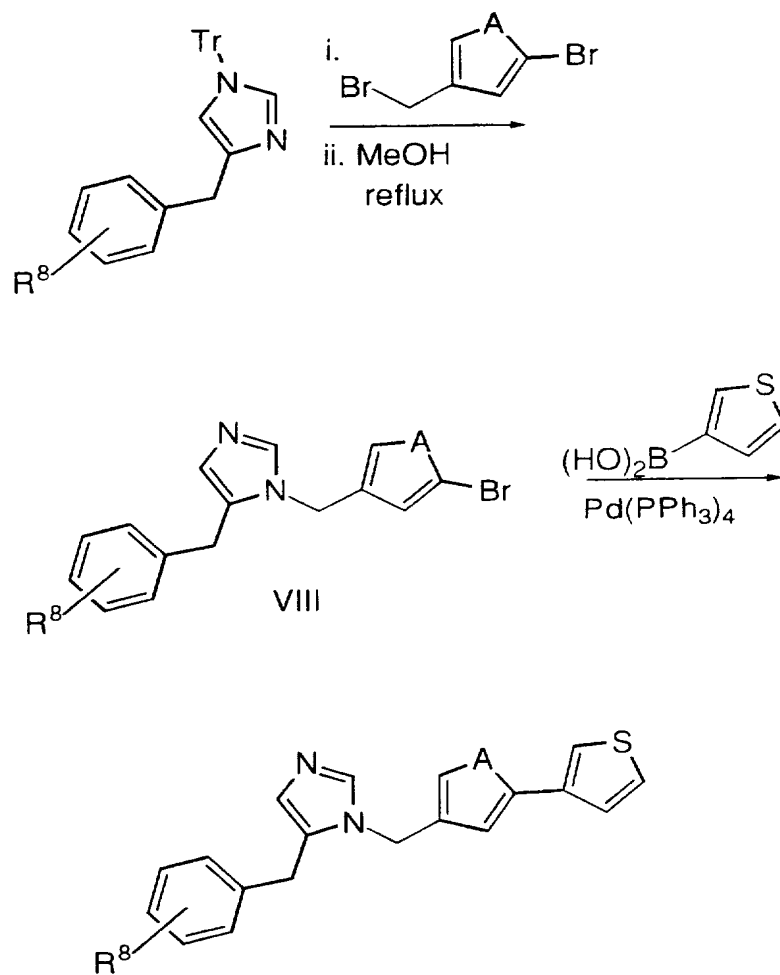
- 48 -

SCHEME 5 (continued)

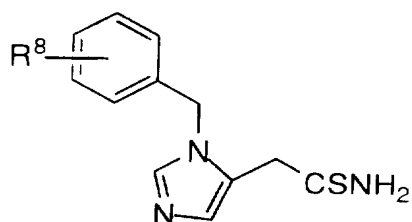
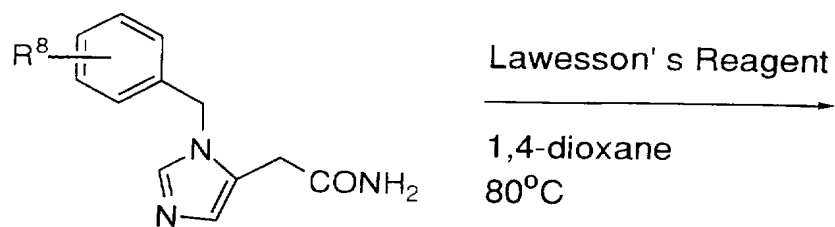
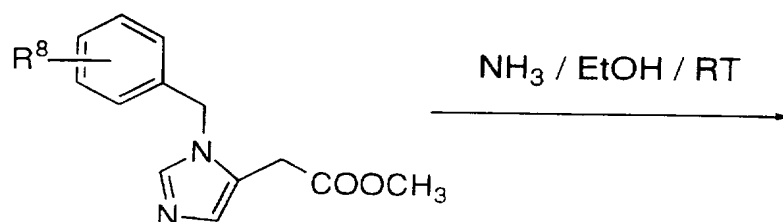
- 49 -

SCHEME 6

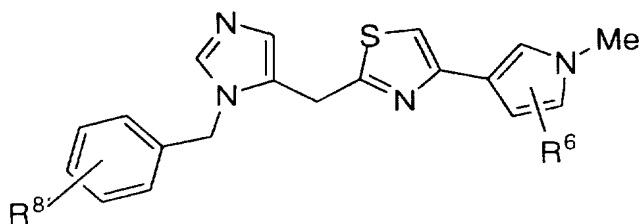
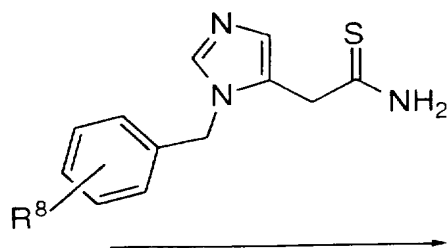
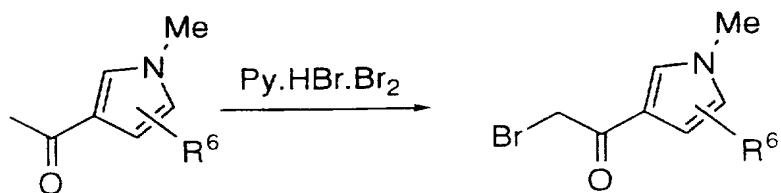
- 50 -

SCHEME 7

- 51 -

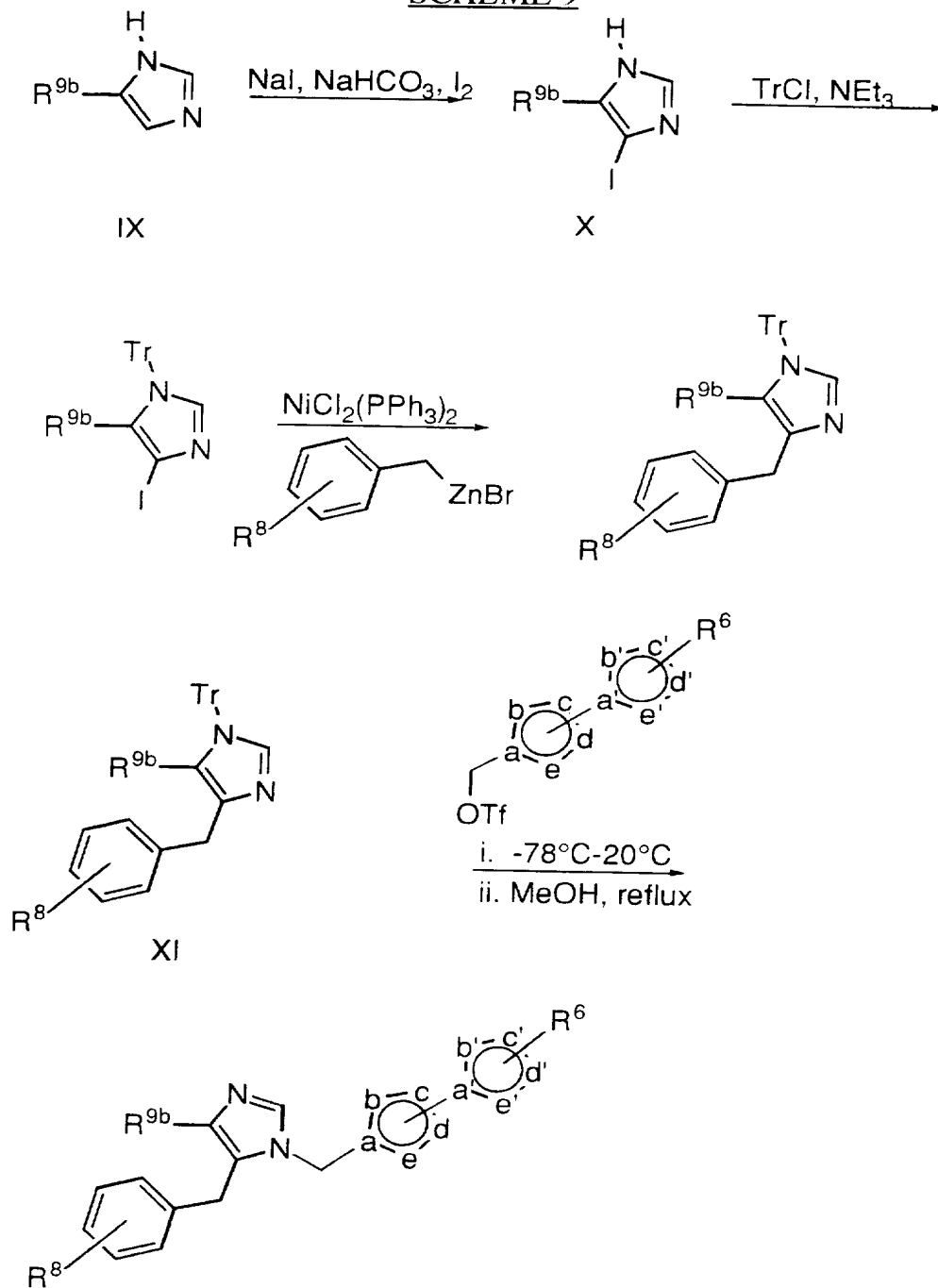
SCHEME 8

- 52 -

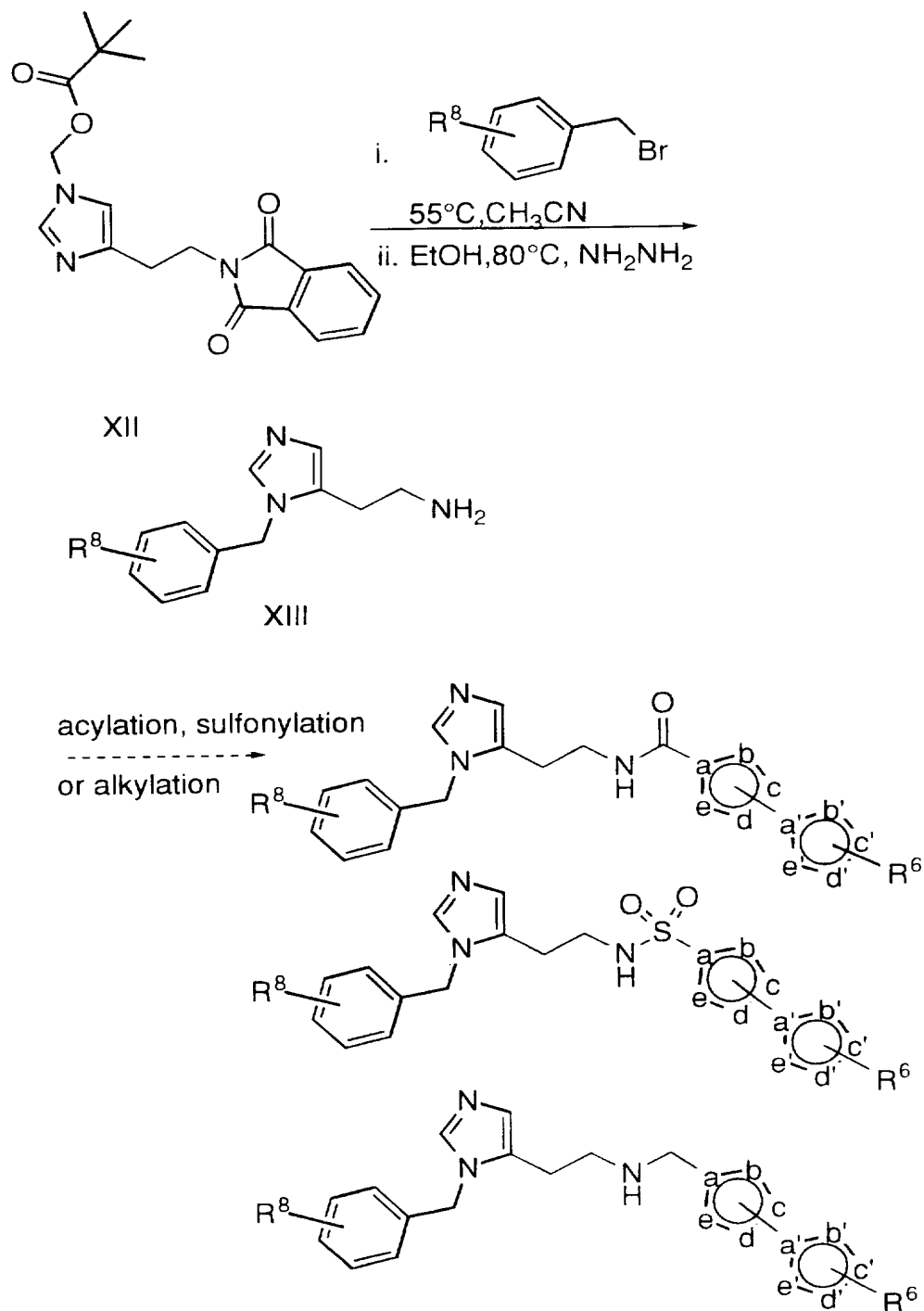
SCHEME 8 (continued)

- 53 -

## SCHEME 9

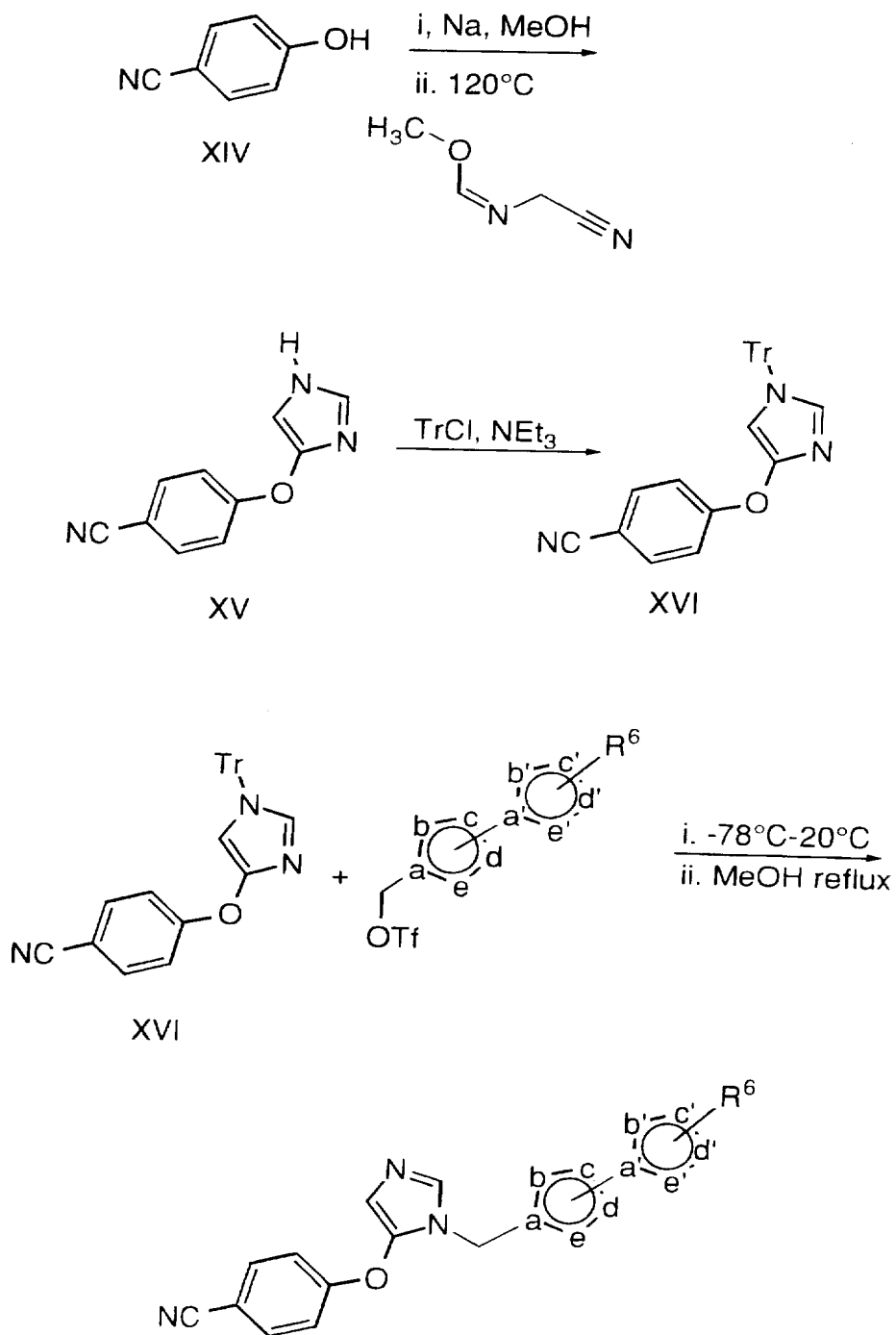


- 54 -

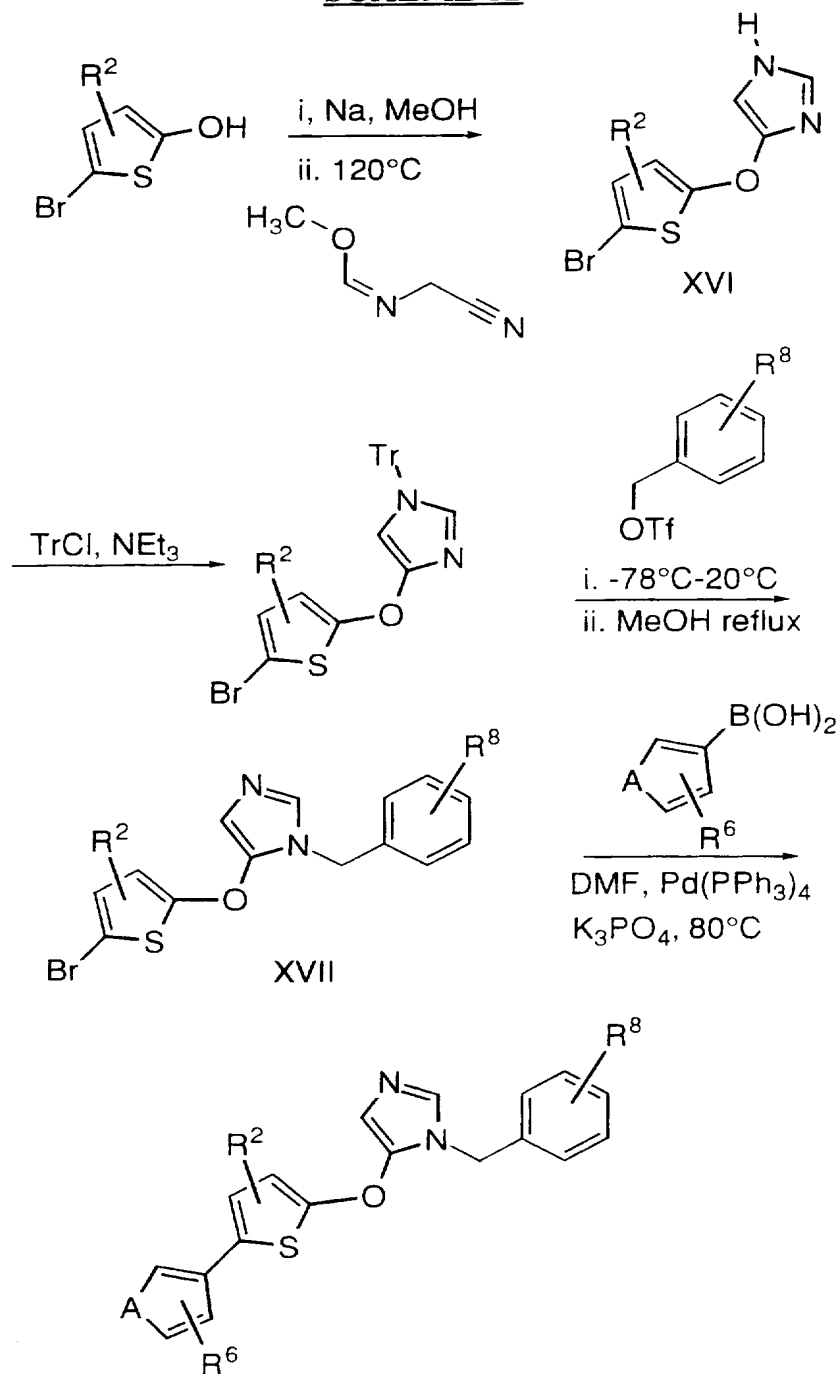
SCHEME 10



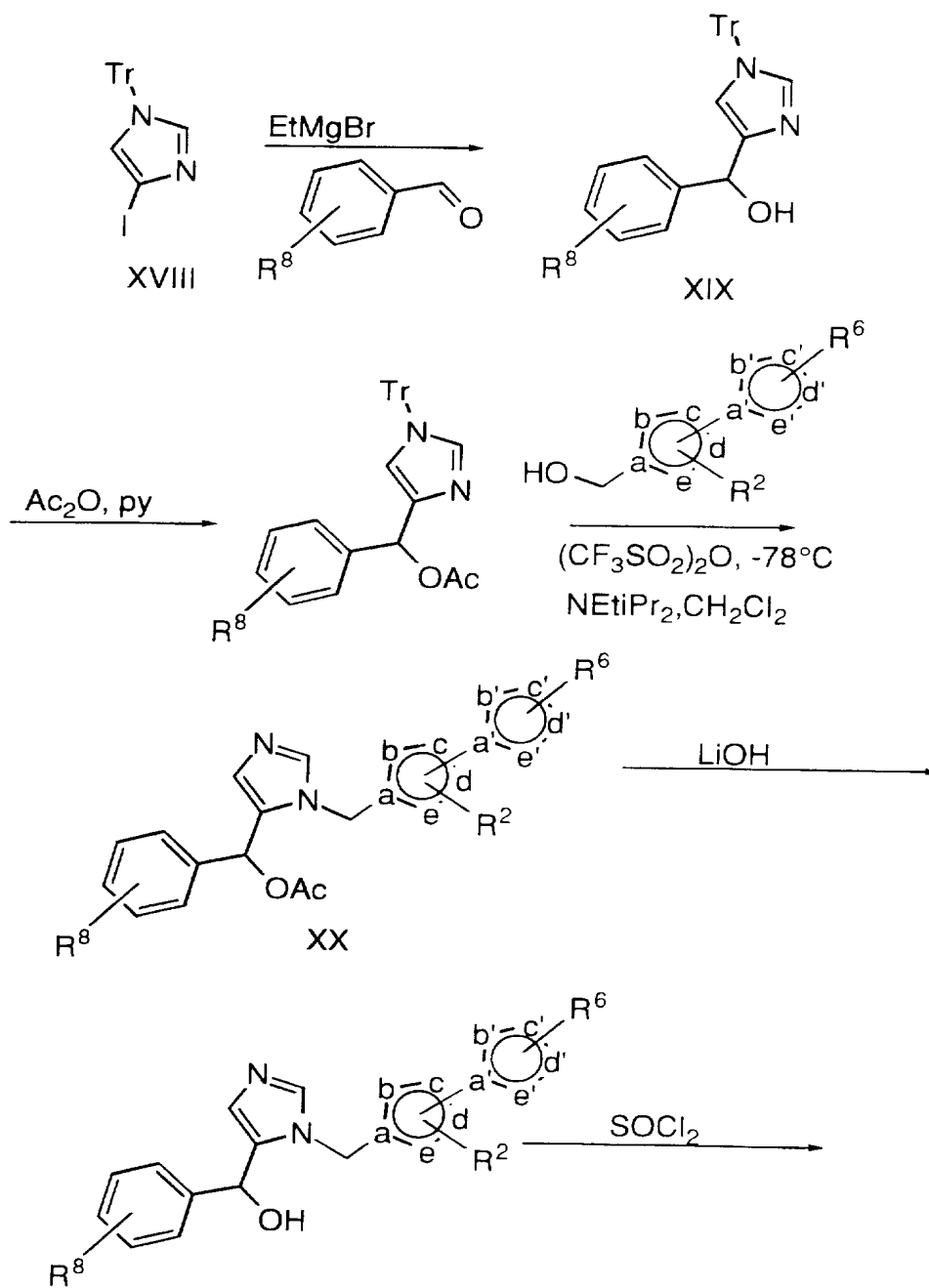
- 55 -

SCHEME 11

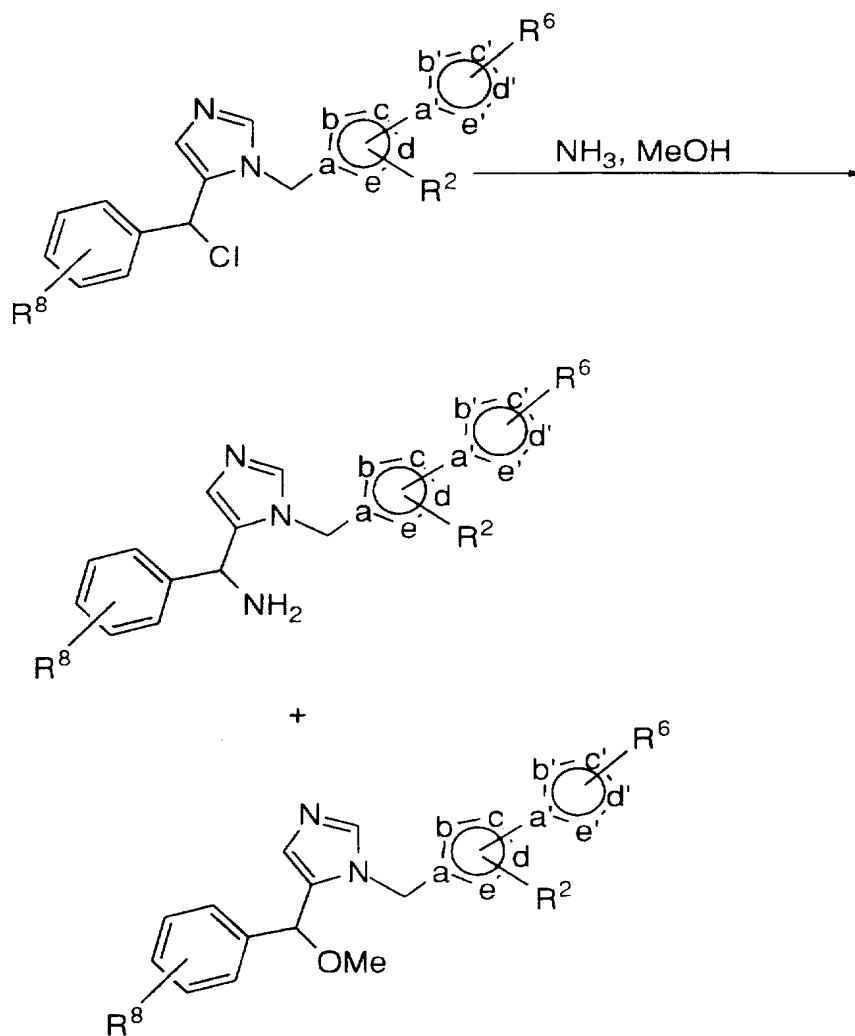
- 56 -

SCHEME 12

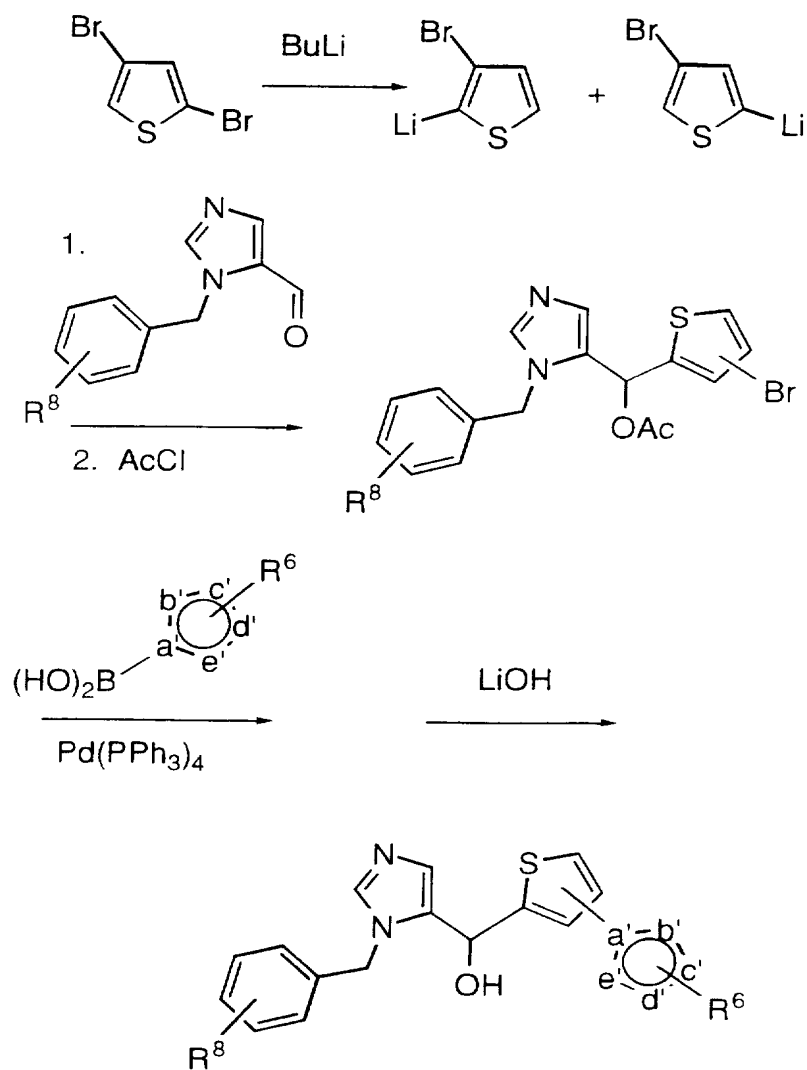
- 57 -

SCHEME 13

- 58 -

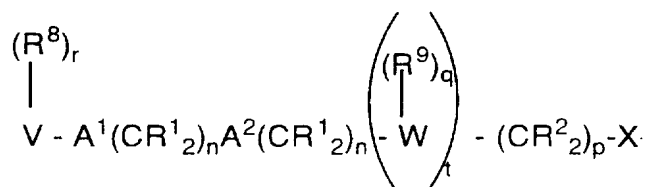
SCHEME 13 (continued)

- 59 -

SCHEME 14

- 60 -

Schemes 15-24 illustrate reactions wherein the moiety



incorporated in the compounds of the instant invention is represented by other than a substituted imidazole-containing group.

- 5            Thus, the intermediates whose synthesis are illustrated in Schemes hereinabove and other biheteroaryl intermediates obtained commercially or readily synthesized, can be coupled with a variety of aldehydes. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in
- 10   Organic Syntheses, **1988**, 67, 69-75, from the appropriate amino acid (Scheme 15). Metal halogen exchange chemistry (Scheme 14) may be employed when manipulating the aldehydes. Alternatively, Grignard chemistry may be utilized, as shown in Scheme 15. Thus, Suzuki
- 15   coupling provides, for example, the pyrrole containing biheteroaryl XXI. Reaction of the intermediate XXI with a Grignard reagent provides the N-pyrrolylmagnesium derivative **XXIa**, which is then reacted with an aldehyde to provide the C-alkylated instant compound XXII. The product **XXII** can be deoxygenated by methods known in the art, such as a catalytic hydrogenation, then deprotected with
- 20   trifluoroacetic acid in methylene chloride to give the final compound **XXIIa**. The final product **XXII** may be isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine **XXII** can further be selectively protected to obtain **XXIII**, which can subsequently be reductively alkylated with a
- 25   second aldehyde to obtain XXIV. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole **XXV** can be accomplished by literature procedures.

- 30            Scheme 16 illustrates the use of in situ formation of a lithium anion of a suitably substituted N-alkyl pyrrole to provide the C-alkylated compound of the instant invention.

- 61 -

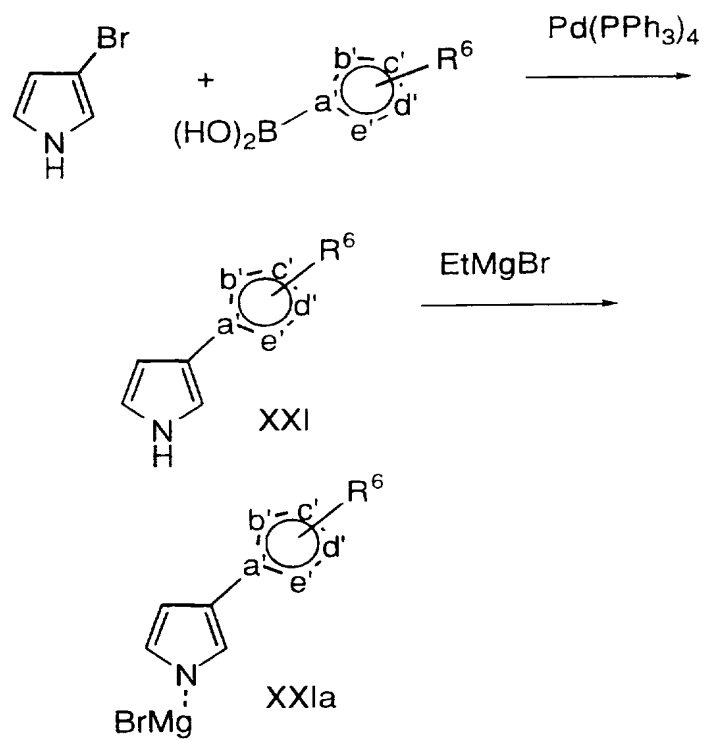
If the biheteroaryl subunit is reductively alkylated with an aldehyde which also has a protected hydroxyl group, such as **XXVI** in Reaction Scheme 17, the protecting groups can be subsequently removed to unmask the hydroxyl group (Reaction Schemes 17, 18). The alcohol  
5 can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as Grignard reagents, to obtain secondary alcohols such as **XXX**. In addition, the fully deprotected amino alcohol **XXXI** can be reductively alkylated (under conditions described previously) with a variety of  
10 aldehydes to obtain secondary amines, such as **XXXII** (Reaction Scheme 18), or tertiary amines.

The Boc protected amino alcohol **XXVIII** can also be utilized to synthesize 2-aziridinylmethylbiheteroaryl such as **XXXIII** (Reaction Scheme 19). Treating **XXVIII** with 1,1'-sulfonyldiimidazole  
15 and sodium hydride in a solvent such as dimethylformamide led to the formation of aziridine **XXXIII**. The aziridine is reacted with a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product **XXXIV**.

In addition, the biheteroaryl subunit can be reacted with  
20 aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as **XL**, as shown in Reaction Scheme 20. When R' is an aryl group, **XL** can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce **XLI**. Alternatively, the amine protecting group in  
25 **XL** can be removed, and O-alkylated phenolic amines such as **XLII** produced.

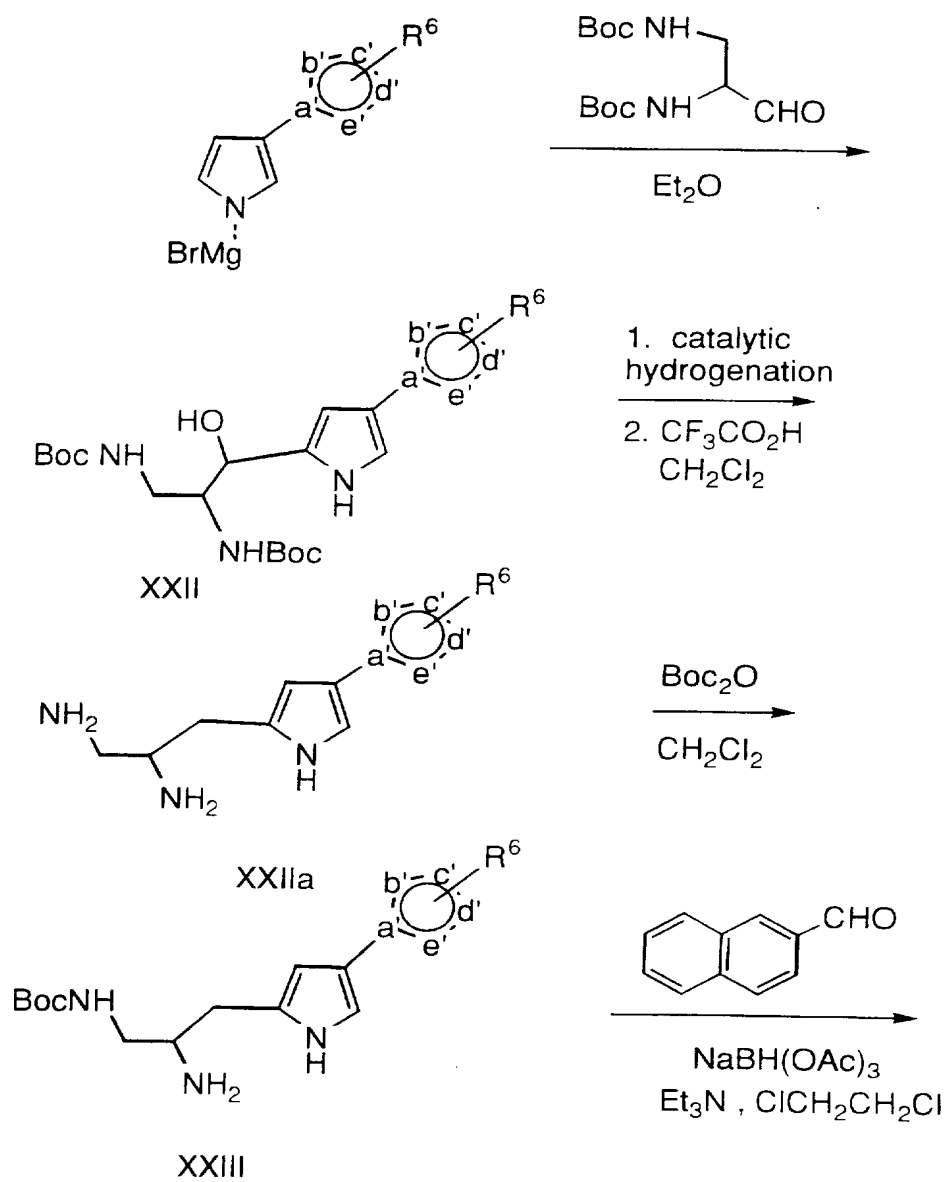
Schemes 21-24 illustrate syntheses of suitably substituted aldehydes useful in the syntheses of the instant compounds wherein the variable W is present as a pyridyl moiety. Similar synthetic strategies  
30 for preparing alkanols that incorporate other heterocyclic moieties for variable W are also well known in the art.

- 62 -

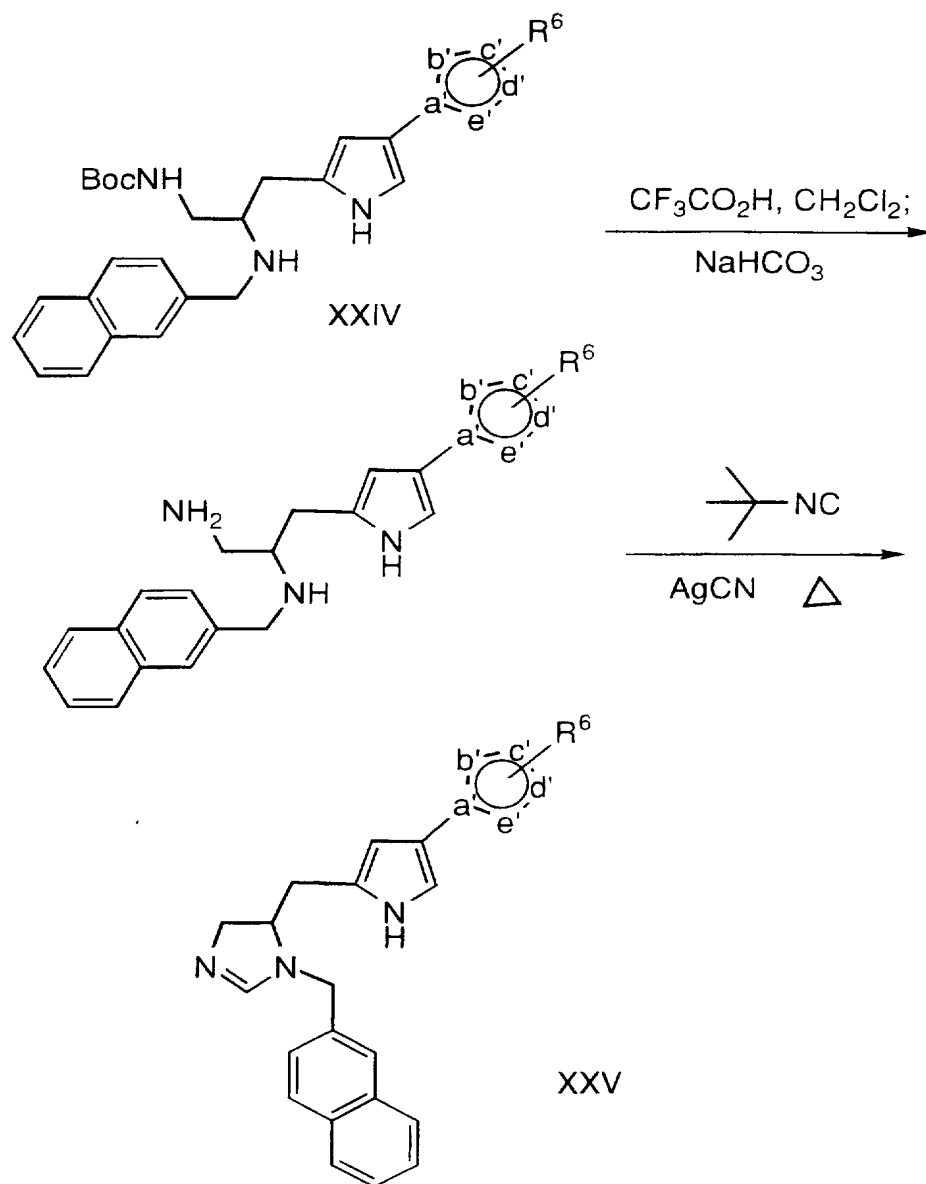
SCHEME 15



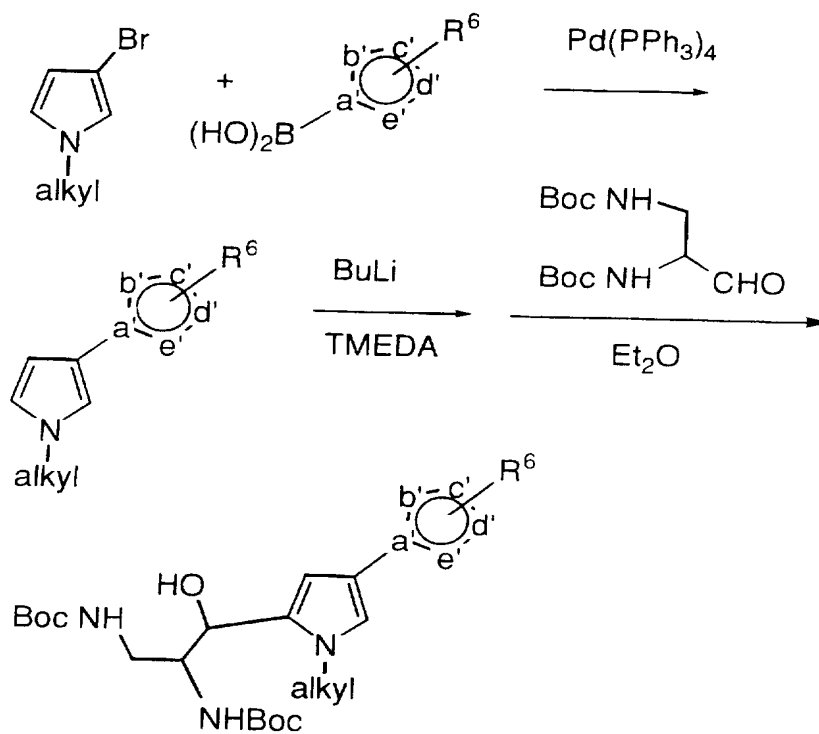
- 63 -

SCHEME 15 (continued)

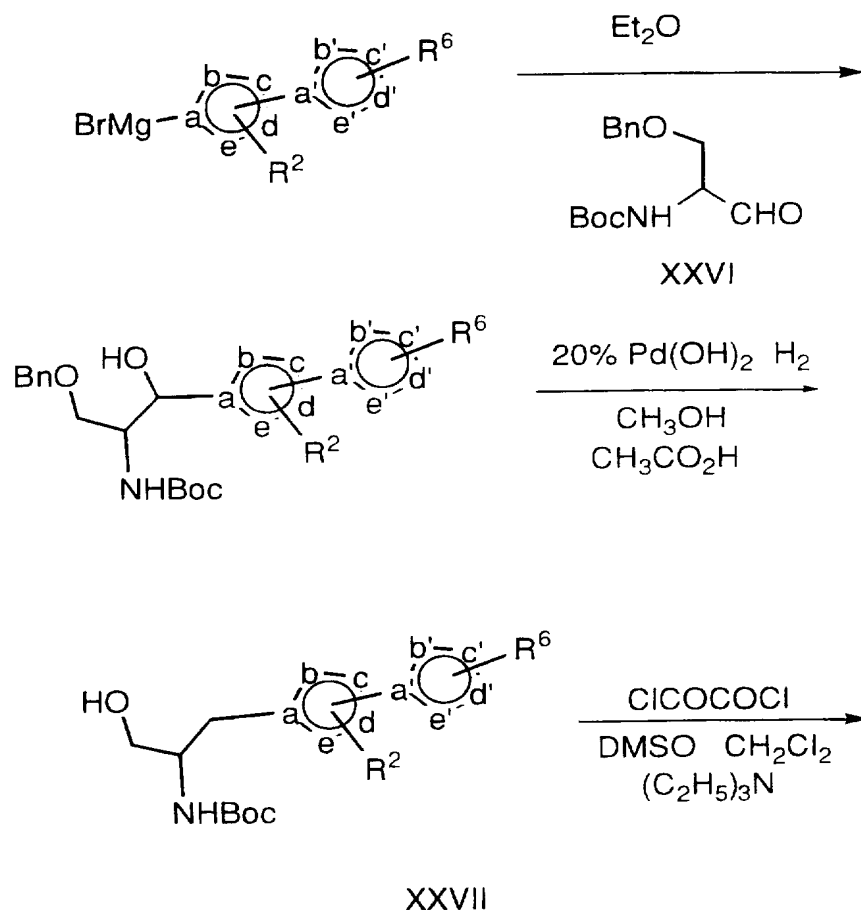
- 64 -

SCHEME 15 (continued)

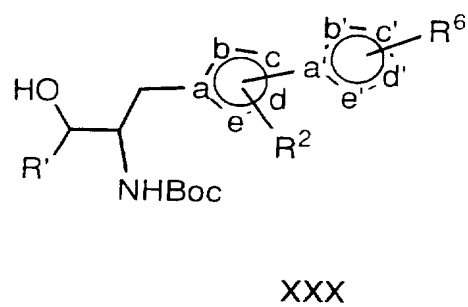
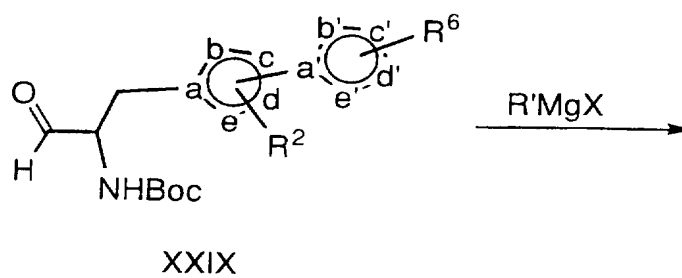
- 65 -

SCHEME 16

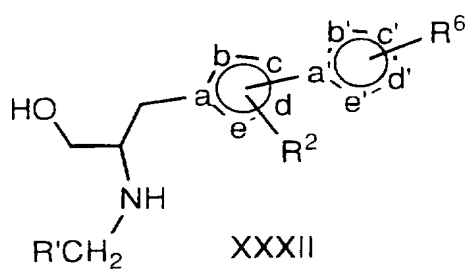
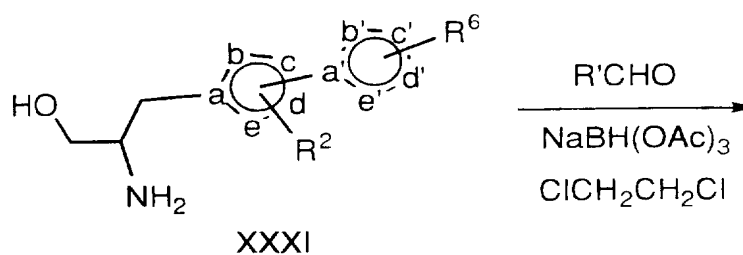
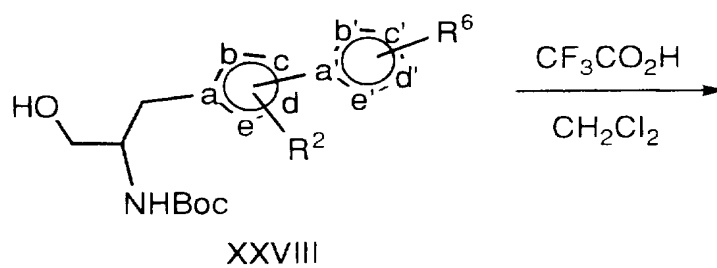
- 66 -

SCHEME 17

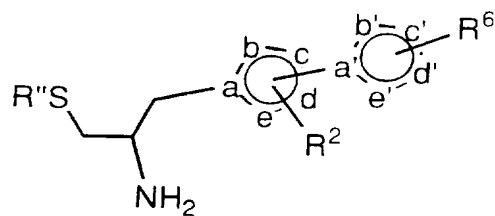
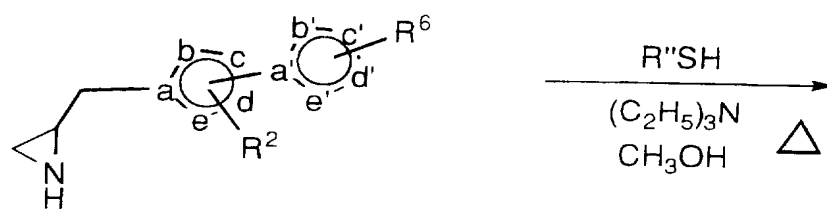
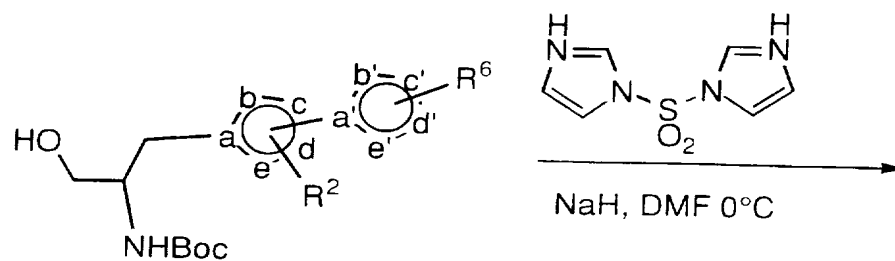
- 67 -

SCHEME 17 (CONTINUED)

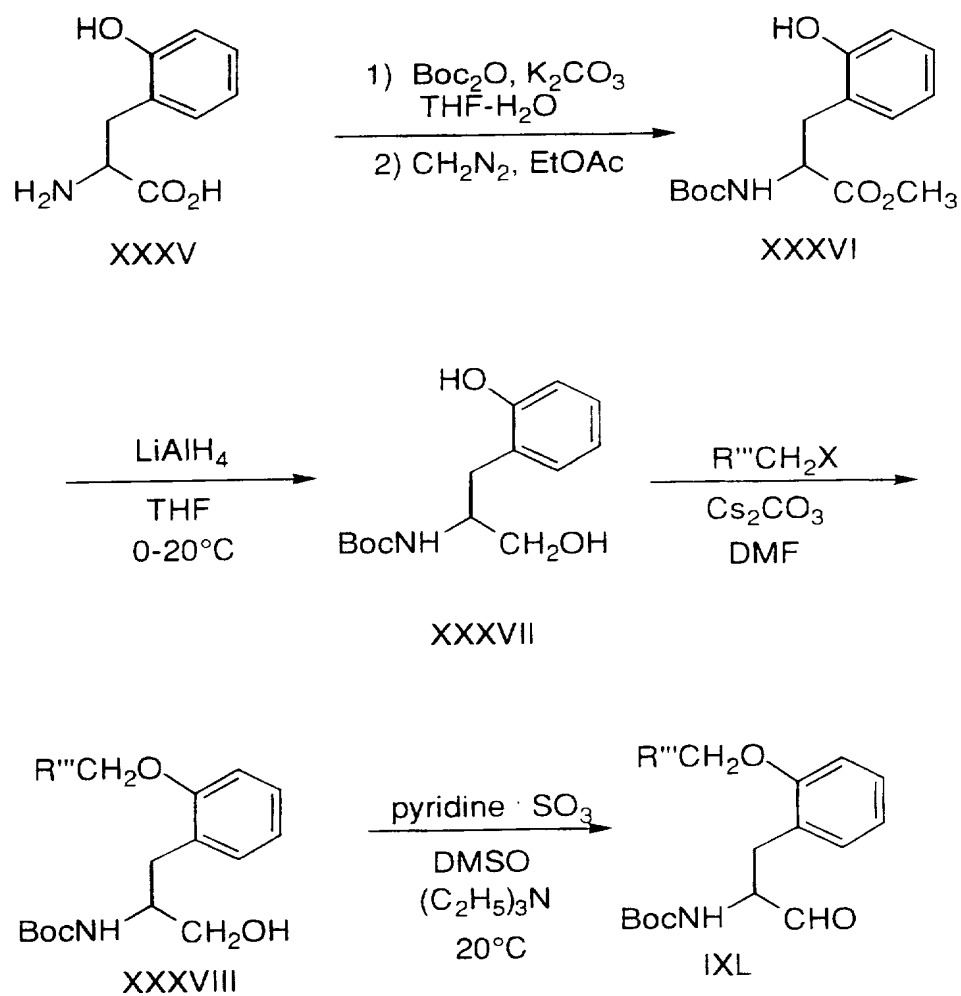
- 68 -

SCHEME 18

- 69 -

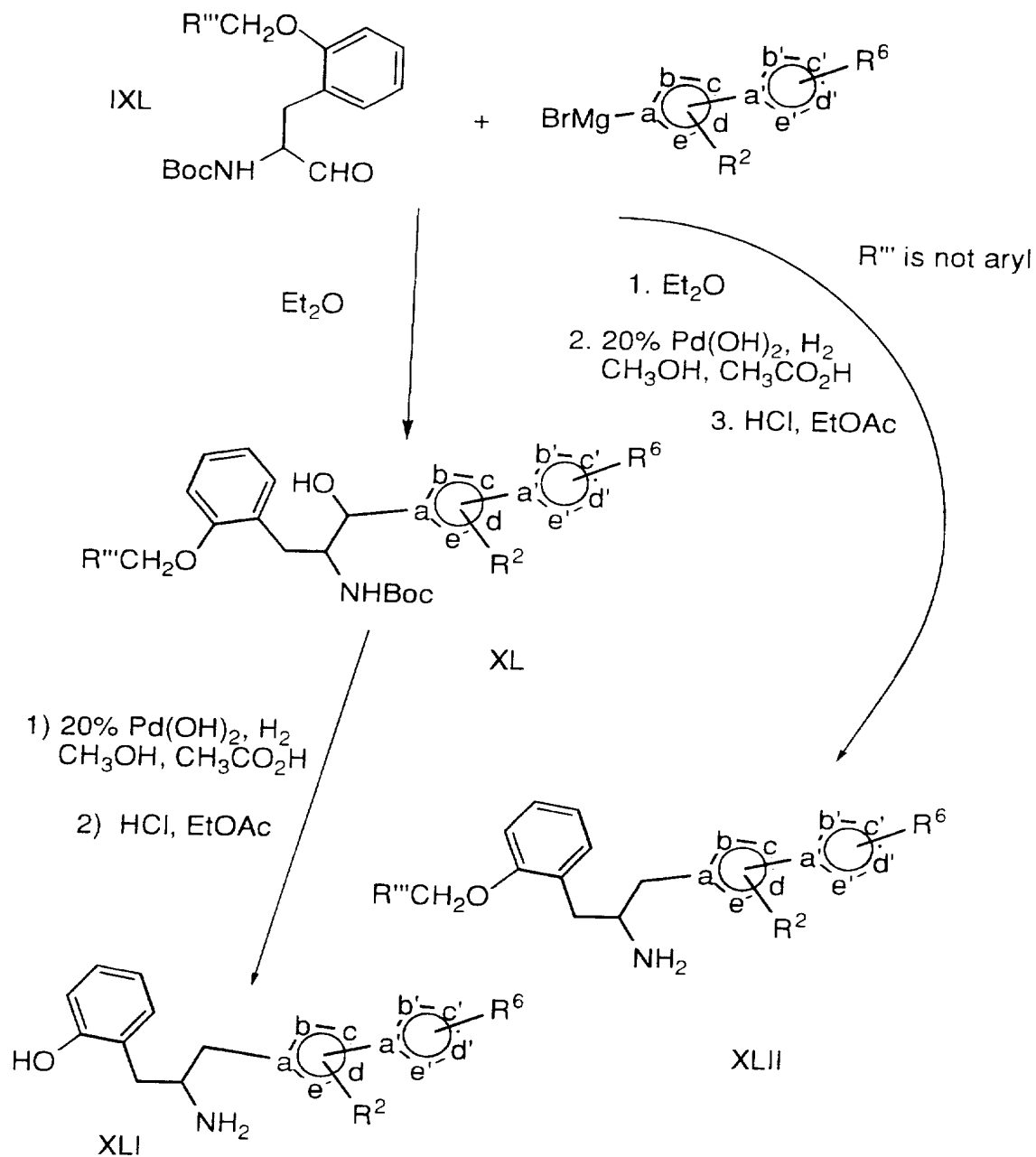
SCHEME 19

- 70 -

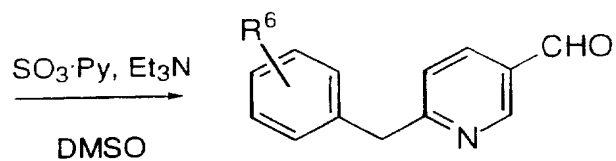
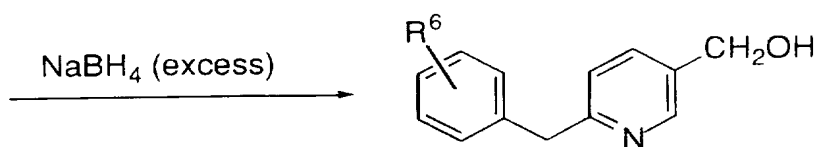
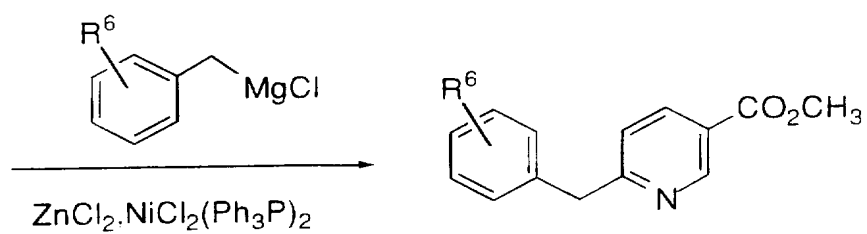
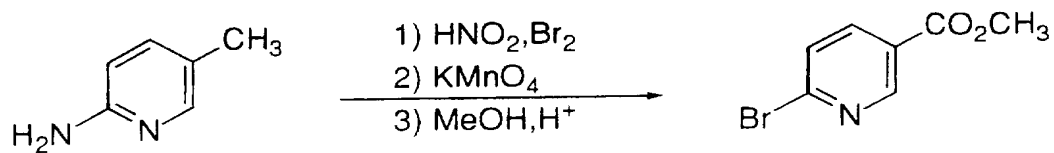
SCHEME 20



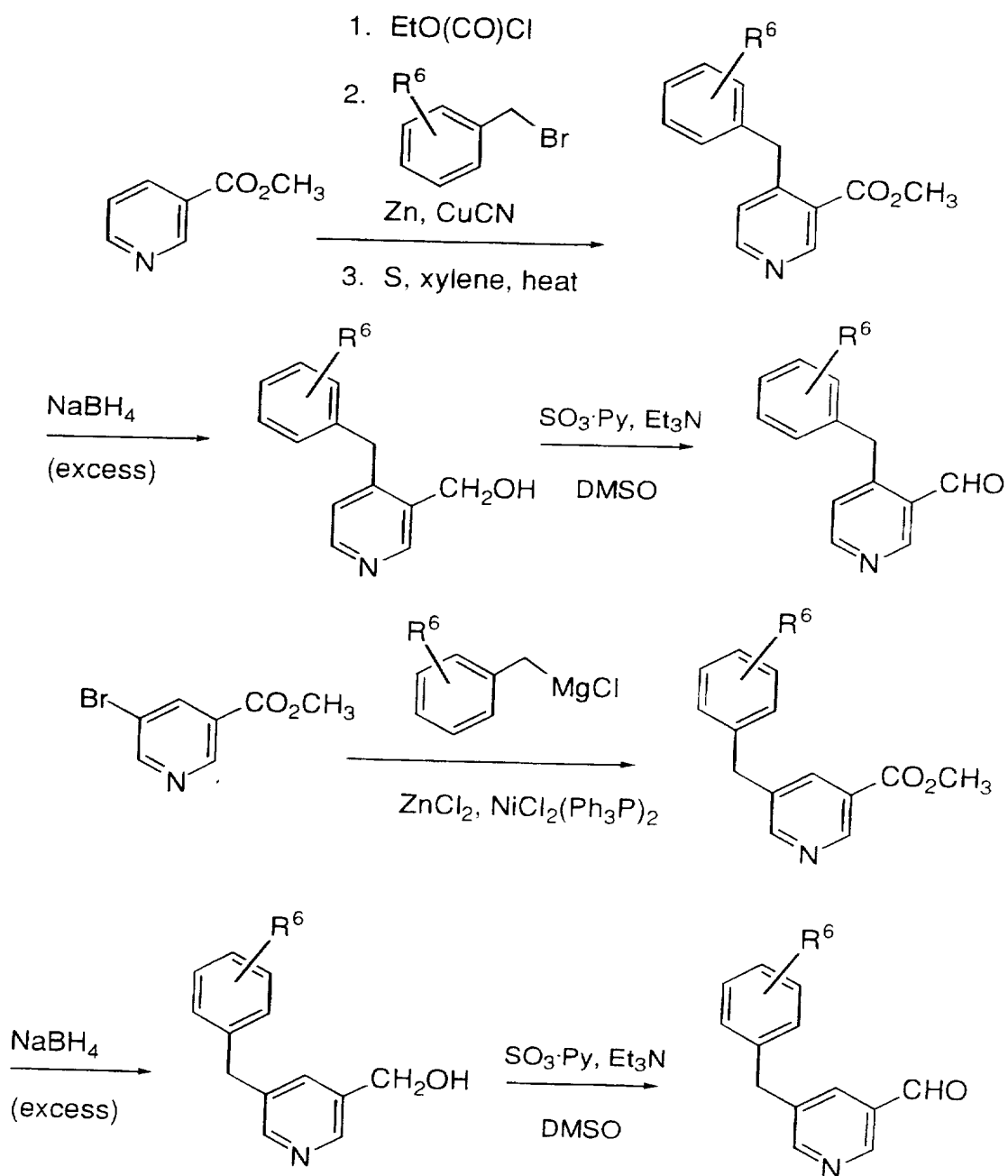
- 71 -

SCHEME 20 (continued)

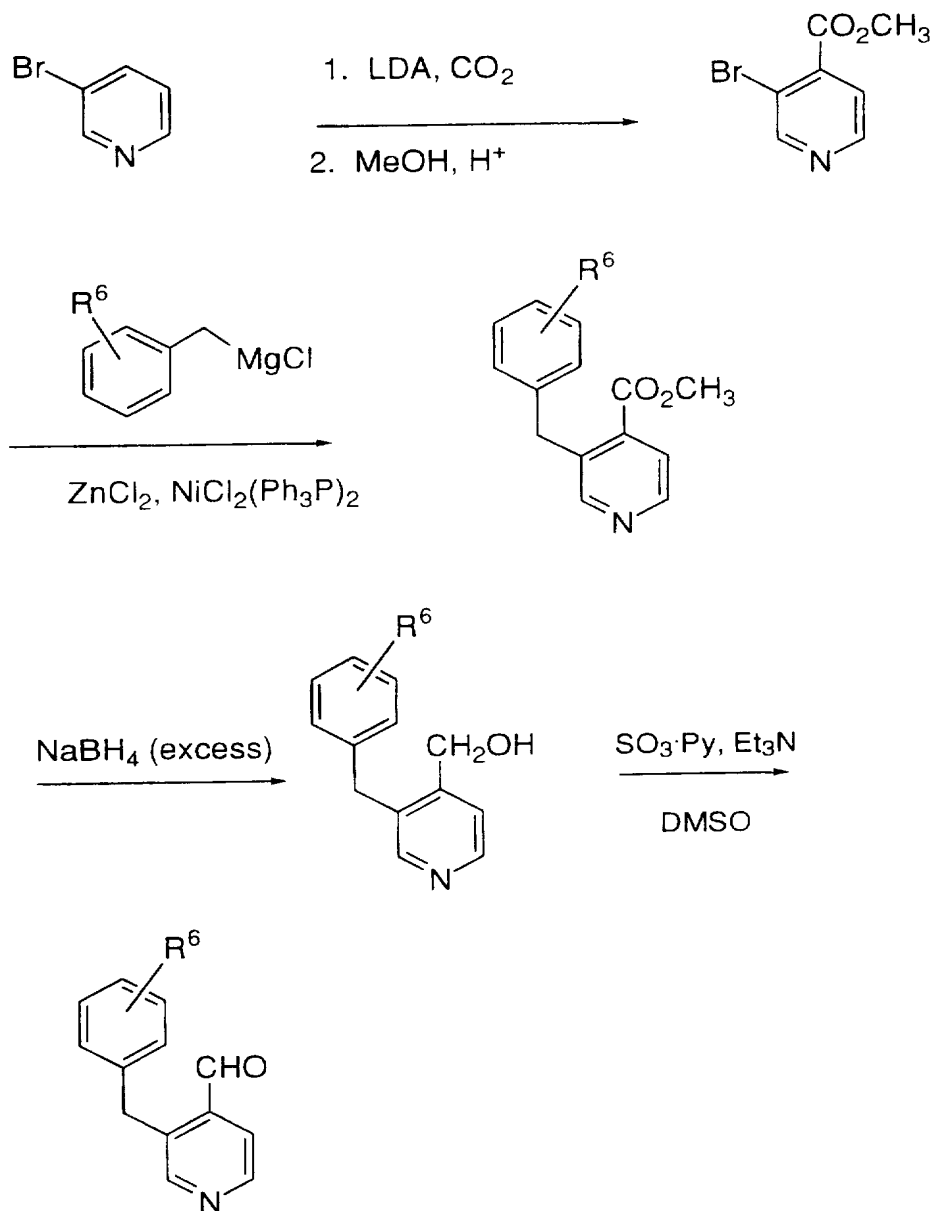
- 72 -

SCHEME 21

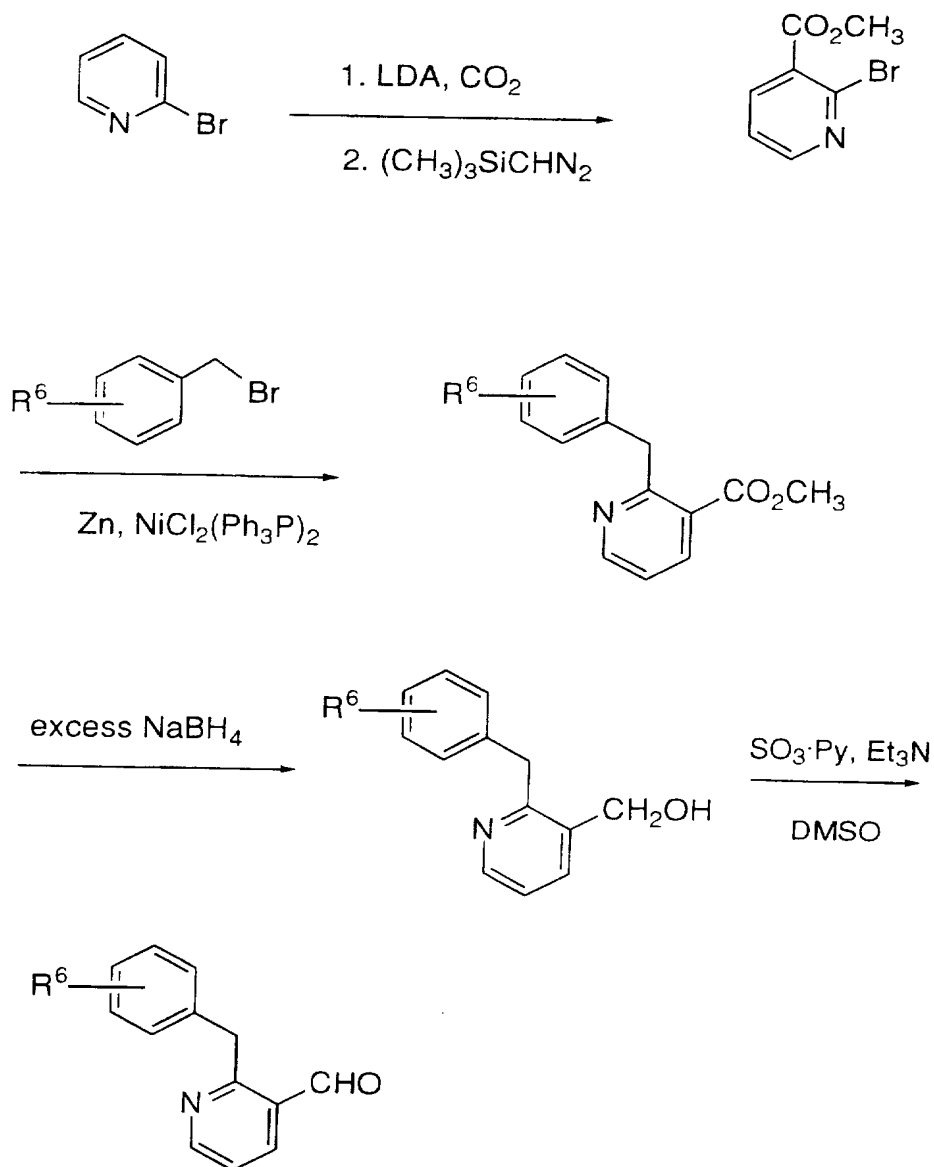
- 73 -

SCHEME 22

- 74 -

SCHEME 23

- 75 -

SCHEME 24

5 The instant compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer. Examples of the type of cancer which may be treated with the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine

- 76 -

pancreatic carcinoma, myeloid leukemias and neurological tumors. Such tumors may arise by mutations in the *ras* genes themselves, mutations in the proteins that can regulate Ras activity (i.e., neurofibromin (NF-1), neu, scr, abl, lck, fyn) or by other mechanisms.

5           The compounds of the instant invention inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. The instant compounds may also inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55:4575-4580 (1995)). Such anti-angiogenesis properties of the  
10 instant compounds may also be useful in the treatment of certain forms of blindness related to retinal vascularization.

          The compounds of this invention are also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic  
15 mutation in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the compounds of the invention to a mammal in need of such treatment. For example, a component of NF-1 is a benign proliferative disorder.

20           The instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis delta and related viruses (J.S. Glenn et al. *Science*, 256:1331-1333 (1992)).

          The compounds of the instant invention are also useful in  
25 the prevention of restenosis after percutaneous transluminal coronary angioplasty by inhibiting neointimal formation (C. Indolfi et al. *Nature medicine*, 1:541-545(1995)).

          The instant compounds may also be useful in the treatment and prevention of polycystic kidney disease (D.L. Schaffner et al.  
30 *American Journal of Pathology*, 142:1051-1060 (1993) and B. Cowley, Jr. et al. *FASEB Journal*, 2:A3160 (1988)).

          The instant compounds may also be useful for the treatment of fungal infections.

          The compounds of this invention may be administered

- 77 -

to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The  
5 compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for  
10 example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral  
15 administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use,  
20 sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The compounds of the instant invention may also be co-administered with other well known therapeutic agents that are  
25 selected for their particular usefulness against the condition that is being treated. For example, the instant compounds may be useful in combination with known anti-cancer and cytotoxic agents. Similarly, the instant compounds may be useful in combination with agents that are effective in the treatment and prevention of NF-1, retinosis,  
30 polycystic kidney disease, infections of hepatitis delta and related viruses and fungal infections.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within

- 78 -

its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

5 The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacolo-  
10 gically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's blood-stream by local bolus injection.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific  
15 amounts, as well as any product which results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally  
20 varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg  
25 of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The compounds of the instant invention are also useful as a component in an assay to rapidly determine the presence and  
30 quantity of farnesyl-protein transferase (FPTase) in a composition. Thus the composition to be tested may be divided and the two portions contacted with mixtures which comprise a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate and, in one of the mixtures,



- 79 -

a compound of the instant invention. After the assay mixtures are incubated for an sufficient period of time, well known in the art, to allow the FPTase to farnesylate the substrate, the chemical content of the assay mixtures may be determined by well known immuno-  
5 logical, radiochemical or chromatographic techniques. Because the compounds of the instant invention are selective inhibitors of FPTase, absence or quantitative reduction of the amount of substrate in the assay mixture without the compound of the instant invention relative to the presence of the unchanged substrate in the assay  
10 containing the instant compound is indicative of the presence of FPTase in the composition to be tested.

It would be readily apparent to one of ordinary skill in the art that such an assay as described above would be useful in identifying tissue samples which contain farnesyl-protein transferase and quantitat-  
15 ing the enzyme. Thus, potent inhibitor compounds of the instant invention may be used in an active site titration assay to determine the quantity of enzyme in the sample. A series of samples composed of aliquots of a tissue extract containing an unknown amount of farnesyl-protein transferase, an excess amount of a known substrate of FPTase  
20 (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate are incubated for an appropriate period of time in the presence of varying concentrations of a compound of the instant invention. The concentration of a sufficiently potent inhibitor (i.e., one that has a  $K_i$  substantially smaller than the concentration of enzyme in  
25 the assay vessel) required to inhibit the enzymatic activity of the sample by 50% is approximately equal to half of the concentration of the enzyme in that particular sample.

### EXAMPLES

30 Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

- 80 -

EXAMPLE 1

1-(5-(Thien-2'-yl)thien-2-ylmethyl)-5-(4-cyanobenzyl)imidazole  
5 trifluoroacetic acid salt

---

Step A: 1-Trityl-4-(4-cyanobenzyl)-imidazole

To a suspension of activated zinc dust (3.57g, 54.98 mmol) in THF (50 mL) was added dibromoethane (0.315 mL, 3.60 mmol) and the reaction stirred under argon for 45 minutes, at 10 20°C. The suspension was cooled to 0°C and a-bromo-p-tolunitrile (9.33g, 47.6 mmol) in THF (100 mL) was added dropwise over a period of 10 minutes. The reaction was then allowed to stir at 20°C for 6 hours and bis(triphenylphosphine)Nickel II chloride (2.40g, 15 3.64 mmol) and 4-iodotritylimidazole (15.95g, 36.6 mmol) were added in one portion. The resulting mixture was stirred 16 hours at 20°C and then quenched by addition of saturated NH<sub>4</sub>Cl solution (100 mL) and the mixture stirred for 2 hours. Saturated aq. NaHCO<sub>3</sub> solution was added to give a pH of 8 and the solution was 20 extracted with EtOAc (2 x 250 mL), dried (MgSO<sub>4</sub>) and the solvent evaporated in vacuo. The residue was chromatographed (Silica gel, 0-20% EtOAc inCH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound as a white solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400Mz) δ (7.54 (2H, d, J=7.9Hz), 7.38(1H, s), 25 7.36-7.29 (11H, m), 7.15-7.09(6H, m), 6.58(1H, s) and 3.93(2H, s) ppm.

Step B: 5-(Thien-2-yl)-thiophene-2-carboxaldehyde

To a solution of thien-2-ylboronic acid (0.939 g, 7.34 mmol) and Na<sub>2</sub>CO<sub>3</sub> (2.40 g, 22.6 mmol) in water (75 mL) 30 is added p-dioxane (75 mL). This mixture is treated sequentially with 5-carboxy-2-thiophenecarboxaldehyde (1.43g, 7.48 mmol) and palladium (II) acetate (151 mg, 0.673 mmol) and allowed to

- 81 -

stir at ambient temperature for 16 hours. The solvent is evaporated in vacuo. To the residue is added EtOAc (400 mL) and water (300 mL). The aqueous layer is acidified to pH 1 with 1.0 N aq. HCl. The aqueous layer is extracted with EtOAc (2 x 200 mL). The  
5 organic extracts are combined, washing with brine (200 mL), 5% aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (200 mL), sat. aq. NaCl (200 mL), drying (Na<sub>2</sub>SO<sub>4</sub>), and the solvent evaporation in vacuo affords the title compound.

Step C: 5-(Thien-2-yl)-2-hydroxymethylthiophene  
10 To a solution of 5-(thien-2'-yl)-thiophen-2-ylcarboxaldehyde (1.11 g, 5.73 mmol) in THF (25 mL) at 0°C is added 1.0 M lithium aluminum hydride in tetrahydrofuran (12.0 mL, 12.0 mmol) over 10 minutes. The reaction is allowed to stir at ambient temperature for 3 hours. The reaction is cooled to 0°C, and  
15 water (0.5 mL), 4 N aq. NaOH (0.5 mL), and water (1.5 mL) are added sequentially. The reaction is filtered through a pad of Celite and the filtrate is evaporated in vacuo. The residue is chromatographed to afford the title compound.

Step D: 1-(5-(Thien-2-yl)thien-2-ylmethyl)-5-(4-cyanobenzyl)imidazole trifluoroacetic acid salt  
20 To a solution of 5-(thien-2'-yl)-2-hydroxymethylthiophene (283 mg, 1.44 mmol) and diisopropylethylamine (0.260 mL, 1.49 mmol) in dichloromethane (6.0 mL) at -78°C is added  
25 trifluoromethanesulfonic anhydride (0.250 mL, 1.49 mmol) and the mixture stirred at -78°C for 1 hour. To this mixture is added a solution of 1-trityl-4-(4-cyanobenzyl)imidazole (613 mg, 1.44 mmol) in dichloromethane (6.0 mL). The mixture is allowed to  
30 warm to ambient temperature and stirred for 2 hours. The solvent is evaporated in vacuo. The residue is dissolved in methanol (15 mL), heated at reflux for 1 hour, and the solvent is evaporated in vacuo. The residue is partitioned between CH<sub>2</sub>Cl<sub>2</sub> and sat. aq. NaHCO<sub>3</sub> solution. The organic layer is dried, (Na<sub>2</sub>SO<sub>4</sub>) and the solvent is evaporated in vacuo. The residue is purified by preparative HPLC,

- 82 -

(gradient elution, 95 :5 to 5:95% water:acetonitrile containing 0.1% trifluoroacetic acid) to afford the title compound as a trifluoroacetic acid salt.

5

EXAMPLE 2

1-(4-Cyanobenzyl)-5-(5-(1-methylpyrrol-2-yl)-thiazol-2-ylmethyl)imidazole

---

- 10 Step A:     1H-Imidazole-4-acetic acid methyl ester hydrochloride  
A solution of 1H-imidazole-4-acetic acid hydrochloride (4.00g, 24.6 mmol) in methanol (100 mL) was saturated with gaseous hydrogen chloride. The resulting solution was allowed to stand at room temperature for 18 hours. The solvent was  
15 evaporated in vacuo to afford the title compound as a white solid.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz) δ 8.85(1H, s), 7.45(1H, s), 3.89(2H, s) and 3.75(3H, s) ppm.

- 20 Step B:     1-(Triphenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester  
To a solution of the product from Step A (24.85 g, 0.141 mol) in DMF (115 mL) was added triethylamine (57.2 mL, 0.412 mol) and triphenylmethyl bromide (55.3 g, 0.171 mol) and the suspension was stirred for 24 hours. After this time, the reaction  
25 mixture was diluted with EtOAc and water. The organic phase was washed with sat. aq. NaHCO<sub>3</sub>, dried, (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated in vacuo. The residue was purified by chromatography (Silica gel, 0-100% EtOAc in hexanes) to provide the title compound as a white solid.  
30 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz) δ 7.35(1H, s), 7.31(9H, m), 7.22(6H, m), 6.76(1H, s), 3.68(3H, s) and 3.60(2H, s) ppm.

- 83 -

Step C:      [1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetic acid methyl ester

---

To a solution of the product from Step B (8.00g, 20.9 mmol) in acetonitrile (70 mL) was added 4-cyanobenzyl bromide  
5 (4.10g, 20.92 mmol) and heated at 55°C for 3 hours. The reaction was cooled to room temperature and the resulting imidazolium salt was collected by filtration. The filtrate was heated at 55°C for 18 hours. The reaction mixture was cooled to room temperature and evaporated in vacuo. To the residue was added EtOAc (70 mL) and  
10 the resulting precipitate collected by filtration. The precipitated imidazolium salts were combined, suspended in methanol (100 mL) and heated to reflux for 30 minutes. After this time, the solvent was removed in vacuo. The resulting residue was suspended in EtOAc (75 mL) and the solid isolated by filtration and washed with EtOAc.  
15 The solid was treated with sat. aq. NaHCO<sub>3</sub> solution (300 mL) and CH<sub>2</sub>Cl<sub>2</sub> (300 mL) and stirred at room temperature for 2 hours. The organic layer was separated, dried, (MgSO<sub>4</sub>) and evaporated in vacuo to afford the title compound as a white solid  
<sup>1</sup>HNMR (CDCl<sub>3</sub>, 400MHz) δ 7.65(1H, d, J=8Hz), 7.53(1H, s),  
20 7.15(1H, d, J=8Hz), 7.04(1H, s), 5.24(2H, s), 3.62(3H, s) and 3.45(2H, s) ppm.

Step D:      4-[5-(Aminocarbonylmethyl)imidazol-1-ylmethyl]benzonitrile

---

25 To a 100 mL glass pressure vessel with a stirring bar was added 1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetic acid methyl ester (6.00g, 23.5 mmol) and absolute ethanol (50 mL). This well stirred solution was cooled to -78°C and 50 mL of anhydrous ammonia was condensed in. The vessel was sealed and the mixture  
30 warmed to ambient temperature. This solution was stirred 24 hours at ambient temperature. The excess ammonia was allowed to evaporate and the ethanol was removed in vacuo. The solid residue was triturated with EtOAc and collected on a frit. This material was dried in vacuo to give the title compound as a white solid.

- 84 -

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400MHz) δ 3.25(s, 2H), 5.32(s, 2H), 6.88(s, 1H), 6.96(s, 1H), 7.24(d, j=8Hz, 2H), 7.42(s, 1H), 7.68(s, 1H), 7.83(d, j=8Hz, 2H).

5    Step E:        1-(4-Cyanobenzyl)-5-(aminothiocarbonyl)methyl-1H-imidazole

---

To a 50 mL round bottomed flask with a stirring bar, reflux condenser and an argon inlet was added 4-[5-(aminocarbonylmethyl)imidazol-1-ylmethyl]benzonitrile (0.36g, 1.49 mmol),

- 10    Lawesson's reagent (0.73g, 1.8 mmol) and 1,4-dioxane (10 mL). This well stirred mixture was heated at 80°C for 24 hours. The cooled reaction mixture was concentrated in vacuo and the residue was chromatographed (silica gel, 10% 2-propanol in ammonia saturated CHCl<sub>3</sub>). The title compound was obtained as a yellow, crystalline solid.

15    <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400MHz) δ 3.66(s, 2H), 5.41(s, 2H), 6.85(s, 1H), 7.24(d, j=8Hz, 2H), 7.70(s, 1H), 7.82(d, j=8Hz, 2H), 9.21(s, 1H), 9.56(s, 1H).

20    Step F:        1-(4-Cyanobenzyl)-5-[5-(1-methylpyrrol-2-yl)-thiazol-2-ylmethyl]imidazole

---

To a 25 mL round bottomed flask with a stirring bar reflux condenser and an argon inlet is added 1-(4-cyanobenzyl)-5-(aminothiocarbonyl)methyl-1H-imidazole (0.12g, 0.468 mmol), dry

- 25    THF (10 mL), and N-methyl-α-bromoacetylpyrrole (0.098g, 0.491 mmol). This mixture is heated at 50°C for 7 hours. The cooled reaction mixture is diluted with EtOAc and washed successively with aq. NaHCO<sub>3</sub>, water, and brine. The organic extract is dried, (MgSO<sub>4</sub>) and the solvent is evaporated in vacuo. The residue is
- 30    purified by chromatography to afford the title compound.

- 85 -

EXAMPLE 3*In vitro* inhibition of ras farnesyl transferase

*Assays of farnesyl-protein transferase.* Partially purified  
5 bovine FPTase and Ras peptides (Ras-CVLS, Ras-CVIM and Ras-CAIL)  
were prepared as described by Schaber et al., J. Biol. Chem. 265:14701-  
14704 (1990), Pompliano, et al., Biochemistry 31:3800 (1992) and  
Gibbs et al., PNAS U.S.A. 86:6630-6634 (1989), respectively. Bovine  
FPTase was assayed in a volume of 100  $\mu$ l containing 100 mM *N*-(2-  
10 hydroxy ethyl) piperazine-*N'*-(2-ethane sulfonic acid) (HEPES), pH  
7.4, 5 mM MgCl<sub>2</sub>, 5 mM dithiothreitol (DTT), 100 mM [<sup>3</sup>H]-farnesyl  
diphosphate ([<sup>3</sup>H]-FPP; 740 CBq/mmol, New England Nuclear), 650  
nM Ras-CVLS and 10  $\mu$ g/ml FPTase at 31°C for 60 min. Reactions  
were initiated with FPTase and stopped with 1 ml of 1.0 M HCL in  
15 ethanol. Precipitates were collected onto filter-mats using a TomTec  
Mach II cell harvester, washed with 100% ethanol, dried and counted  
in an LKB  $\beta$ -plate counter. The assay was linear with respect to both  
substrates, FPTase levels and time; less than 10% of the [<sup>3</sup>H]-FPP was  
utilized during the reaction period. Purified compounds were dissolved  
20 in 100% dimethyl sulfoxide (DMSO) and were diluted 20-fold into the  
assay. Percentage inhibition is measured by the amount of incorpora-  
tion of radioactivity in the presence of the test compound when  
compared to the amount of incorporation in the absence of the test  
compound.

25 Human FPTase was prepared as described by Omer  
et al., Biochemistry 32:5167-5176 (1993). Human FPTase activity  
was assayed as described above with the exception that 0.1% (w/v)  
polyethylene glycol 20,000, 10  $\mu$ M ZnCl<sub>2</sub> and 100 nM Ras-CVIM were  
added to the reaction mixture. Reactions were performed for 30 min.,  
30 stopped with 100  $\mu$ l of 30% (v/v) trichloroacetic acid (TCA) in ethanol  
and processed as described above for the bovine enzyme.

The compounds of the instant invention are tested for  
inhibitory activity against human FPTase by the assay described above.

- 86 -

EXAMPLE 4*In vivo* ras farnesylation assay

The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The assay is performed essentially as described in DeClue, J.E. et al., Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluency are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemented with 10% regular DMEM, 2% fetal bovine serum and 400 mCi [<sup>35</sup>S]methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM MgCl<sub>2</sub>/1 mM DTT/10 mg/ml aprotinin/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Aliquots of lysates containing equal numbers of acid-precipitable counts are brought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. et al., J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 µl of a 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 mM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100/0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

30



- 87 -

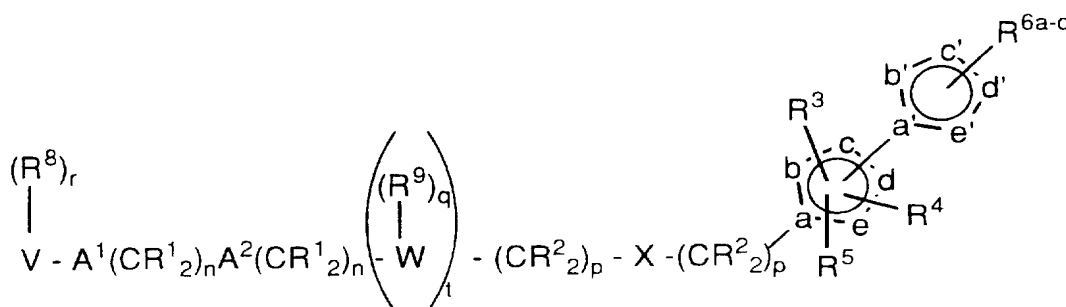
EXAMPLE 5In vivo growth inhibition assay

- 5 To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a *v-ras*, *v-raf*, or *v-mos* oncogene is tested. Cells transformed by v-Raf and v-Mos maybe included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.
- 10 Rat 1 cells transformed with either *v-ras*, *v-raf*, or *v-mos* are seeded at a density of  $1 \times 10^4$  cells per plate (35 mm in diameter) in a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an
- 15 appropriate concentration of the instant compound (dissolved in methanol at 1000 times the final concentration used in the assay). The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photomicrographs are taken 16 days after the cultures are seeded
- 20 and comparisons are made.

- 88 -

WHAT IS CLAIMED IS:

1. A compound which inhibits farnesyl-protein transferase of the formula A:



5

A

wherein:

a is N or C;

10 from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

a' is N or C;

15

from 0-4 of b', c', d' and e' are independently N, NH, O and S, and the remaining b', c', d' and e' atoms are independently CH, provided that if a' is C, then at least one of b', c', d' or e' is independently N, NH, O or S;

20

R<sup>1</sup> and R<sup>2</sup> are independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl,

- 89 -

5 c) C2-C6 alkynyl, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>11</sup>C(O)O-,  
 R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN,  
 NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
 10 unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the  
 substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected  
 from unsubstituted or substituted aryl, heterocyclic,  
 C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,  
 R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-,  
 R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and  
 R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently selected from:

- 15 a) hydrogen,  
 b) unsubstituted or substituted aryl, unsubstituted or  
 substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub>  
 alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl,  
 R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, R<sup>11</sup>C(O)O-,  
 (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-,  
 N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
 20 c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
 d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the  
 substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or  
 substituted aryl, unsubstituted or substituted heterocyclic,  
 C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-,  
 25 R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-  
 C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-  
 NR<sup>10</sup>-;

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

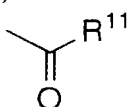
- 30 a) hydrogen,  
 b) unsubstituted or substituted aryl, unsubstituted or  
 substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub>  
 alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl,  
 R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, R<sup>11</sup>C(O)O-,

- 90 -

$(R^{10})_2NC(O)-$ ,  $R^{10}_2N-C(NR^{10})-$ ,  $CN$ ,  $NO_2$ ,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , or  $R^{11}OC(O)NR^{10}-$ ,

- c) unsubstituted  $C_1-C_6$  alkyl,  
 d) substituted  $C_1-C_6$  alkyl wherein the substituent on the  
 5 substituted  $C_1-C_6$  alkyl is selected from unsubstituted or  
 substituted aryl, unsubstituted or substituted heterocyclic,  
 $C_3-C_{10}$  cycloalkyl,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl,  
 $R^{12}O-$ ,  $R^{11}S(O)_m-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  
 $R^{10}_2N-C(NR^{10})-$ ,  $CN$ ,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , and  
 10  $R^{11}OC(O)-NR^{10}-$ ;

$R^7$  is selected from:  $H$ ;  $C_1-4$  alkyl,  $C_3-6$  cycloalkyl, heterocycle, aryl,  
 aroyl, heteroaryl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or  
 substituted with:

- 15 a)  $C_1-4$  alkoxy,  
 b) aryl or heterocycle,  
 c) halogen,  
 d)  $HO$ ,  
 e)   
 f)  $-SO_2R^{11}$ ,  
 20 g)  $N(R^{10})_2$  or  
 h)  $C_1-4$  perfluoroalkyl;

$R^8$  is independently selected from:

- a) hydrogen,  
 25 b) aryl, substituted aryl, heterocycle,  $C_3-C_{10}$  cycloalkyl,  
 $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl, perfluoroalkyl,  $F$ ,  $Cl$ ,  $Br$ ,  
 $R^{10}O-$ ,  $R^{11}S(O)_m-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  
 $R^{10}_2N-C(NR^{10})-$ ,  $CN$ ,  $NO_2$ ,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , or  
 $R^{11}OC(O)NR^{10}-$ , and

- 91 -

- 5 c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, perfluoroalkyl, F, Cl, Br, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NH-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>10</sup>OC(O)NH-;

provided that when R<sup>8</sup> is heterocycle, attachment of R<sup>8</sup> to V is through a substitutable ring carbon;

10 R<sup>9</sup> is independently selected from:

- a) hydrogen,  
 b) C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, Br, R<sup>11</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and  
 15 c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

20

R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

25 R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

30

A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, O, -N(R<sup>10</sup>)-, -S(O)<sub>2</sub>N(R<sup>10</sup>)-, -N(R<sup>10</sup>)S(O)<sub>2</sub>-, or S(O)<sub>m</sub>;

- 92 -

V is selected from:

- a) hydrogen,
  - b) heterocycle,
  - 5 c) aryl,
  - d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
  - e) C<sub>2</sub>-C<sub>20</sub> alkenyl,
- 10 provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;  
provided that when V is heterocycle, attachment of V to R<sup>8</sup> and to A<sup>1</sup> is through a substitutable ring carbon;

15 W is a heterocycle;

X is a bond, -CH=CH-, O, -C(=O)-, -C(O)NR<sup>7</sup>-, -NR<sup>7</sup>C(O)-, -C(O)O-,  
-OC(O)-, -C(O)NR<sup>7</sup>C(O)-, -NR<sup>7</sup>-, -S(O)<sub>2</sub>N(R<sup>10</sup>)-,  
-N(R<sup>10</sup>)S(O)<sub>2</sub>- or -S(=O)<sub>m</sub>-, provided that if a is N, then  
20 X is not O, -C(O)NR<sup>7</sup>-, -C(O)O-, -C(O)NR<sup>7</sup>C(O)-, -S(O)<sub>2</sub>N(R<sup>10</sup>)- or -NR<sup>7</sup>-;

m is 0, 1 or 2;

n is independently 0, 1, 2, 3 or 4;

25 p is independently 0, 1, 2, 3 or 4;

q is 0, 1, 2 or 3;

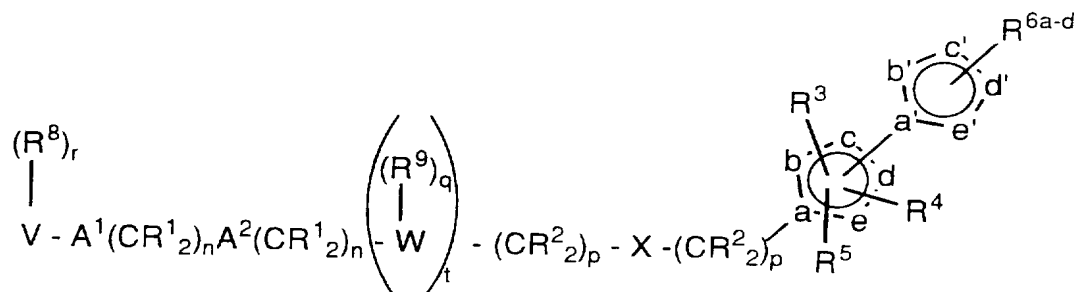
r is 0 to 5, provided that r is 0 when V is hydrogen; and

t is 0 or 1;

30 or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1 of the formula A:

- 93 -



A

wherein:

5 a is N or C;

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

10 a' is N or C;

15 from 0-4 of b', c', d' and e' are independently N, NH, O and S, and the remaining b', c', d' and e' atoms are independently CH, provided that if a' is C, then at least one of b', c', d' or e' is independently N, NH, O or S;

R<sup>1</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>1</sub>-C<sub>6</sub> alkyl;

20 R<sup>2</sup> is independently selected from:

- a) hydrogen,
  - b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>2</sub>-C<sub>6</sub> alkenyl,
  - c) unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the
- 25 substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from

- 94 -

unsubstituted or substituted aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O- and -N(R<sup>10</sup>)<sub>2</sub>;

R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently selected from:

- 5        a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- 10        c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl;
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;
- 15
- 20

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

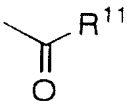
- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- 25        c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl;
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic,
- 30



- 95 -

C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl,  $R^{12}O-$ ,  $R^{11}S(O)_m-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  $R^{10}_2N-C(NR^{10})-$ ,  $CN$ ,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , and  $R^{11}OC(O)-NR^{10}-$ ;

- 5  $R^7$  is selected from: H; C1-4 alkyl, C3-6 cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

- 10 a) C1-4 alkoxy,  
b) aryl or heterocycle,  
c) halogen,  
d) HO,  
e) ,  
f)  $-SO_2R^{11}$ ,  
g)  $N(R^{10})_2$  or  
h) C1-4 perfluoroalkyl;

15

$R^8$  is independently selected from:

- a) hydrogen,  
b) aryl, substituted aryl, heterocycle, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perfluoroalkyl, F, Cl,  $R^{10}O-$ ,  $R^{10}C(O)NR^{10}-$ ,  $CN$ ,  $NO_2$ ,  $(R^{10})_2N-C(NR^{10})-$ ,  $R^{10}C(O)-$ ,  $-N(R^{10})_2$ , or  $R^{11}OC(O)NR^{10}-$ , and  
20 c) C1-C6 alkyl substituted by C1-C6 perfluoroalkyl,  $R^{10}O-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2N-C(NR^{10})-$ ,  $R^{10}C(O)-$ ,  $-N(R^{10})_2$ , or  $R^{11}OC(O)NR^{10}-$ ;

25

provided that when  $R^8$  is heterocycle, attachment of  $R^8$  to V is through a substitutable ring carbon;

$R^9$  is selected from:

- 30 a) hydrogen,  
b) C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perfluoroalkyl, F, Cl,  $R^{11}O-$ ,  $R^{11}S(O)_m-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,

- 96 -

CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and

- 5 c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, CN, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

10 R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

15 R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

20 A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR<sup>10</sup>-, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;

V is selected from:

- 25 a) hydrogen,  
 b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,  
 c) aryl,  
 d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N,  
 30 and  
 e) C<sub>2</sub>-C<sub>20</sub> alkenyl, and

provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;

- 97 -

provided that when V is heterocycle, attachment of V to R<sup>8</sup> and to A<sup>1</sup> is through a substitutable ring carbon;

5 W is a heterocycle selected from pyrrolidinyl, imidazolyl, imidazoliny, pyridinyl, thiazolyl, oxazolyl, indolyl, quinoliny, triazolyl or isoquinoliny;

10 X is a bond, O, -C(=O)-, -CH=CH-, -C(O)NR<sup>7</sup>-, -NR<sup>7</sup>C(O)-, -NR<sup>7</sup>-, -S(O)<sub>2</sub>N(R<sup>10</sup>)-, -N(R<sup>10</sup>)S(O)<sub>2</sub>- or -S(=O)<sub>m</sub>-; provided that if a is N, then X is not O, -C(O)NR<sup>7</sup>-, -S(O)<sub>2</sub>N(R<sup>10</sup>)- or -NR<sup>7</sup>-;

m is 0, 1 or 2;

n is independently 0, 1, 2, 3 or 4;

15 p is independently 0, 1, 2, 3 or 4;

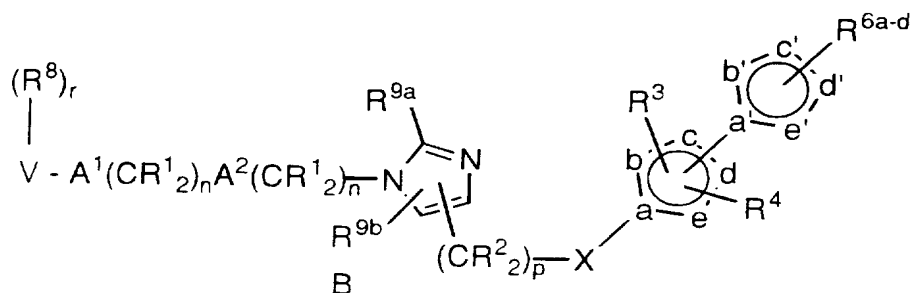
q is 0, 1, 2 or 3;

r is 0 to 5, provided that r is 0 when V is hydrogen; and

t is 0 or 1;

20 or a pharmaceutically acceptable salt thereof.

3. The compound according to Claim 1 of the formula B:



wherein:

25

a is N or C;

- 98 -

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

5 a' is N or C;

from 0-4 of b', c', d' and e' are independently N, NH, O and S, and the remaining b', c', d' and e' atoms are independently CH, provided that if a' is C, then at least one of b', c', d' or e' is independently N, NH, O or S;

R<sup>1</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>1</sub>-C<sub>6</sub> alkyl;

15 R<sup>2</sup> is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>2</sub>-C<sub>6</sub> alkenyl,
- c) unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O- and -N(R<sup>10</sup>)<sub>2</sub>;

R<sup>3</sup> and R<sup>4</sup> are independently selected from:

- 25 a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or

- 99 -

substituted aryl, unsubstituted or substituted heterocyclic, C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl, halogen, C1-C6 perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c) unsubstituted C1-C6 alkyl,
- d) substituted C1-C6 alkyl wherein the substituent on the substituted C1-C6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

R<sup>8</sup> is independently selected from:

- a) hydrogen,
- b) aryl, substituted aryl, heterocycle, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and
- c) C1-C6 alkyl substituted by C1-C6 perfluoroalkyl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

provided that when R<sup>8</sup> is heterocycle, attachment of R<sup>8</sup> to V is through a substitutable ring carbon;

- 100 -

R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, trifluoromethyl and halogen;

- 5 R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

- 10 R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

15

A<sup>1</sup> and A<sup>2</sup> are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR<sup>10</sup>-, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;

V is selected from:

- 20 a) hydrogen,  
b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,  
c) aryl,  
25 d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and  
e) C<sub>2</sub>-C<sub>20</sub> alkenyl, and

- provided that V is not hydrogen if A<sup>1</sup> is S(O)<sub>m</sub> and V is not hydrogen if A<sup>1</sup> is a bond, n is 0 and A<sup>2</sup> is S(O)<sub>m</sub>;  
30 provided that when V is heterocycle, attachment of V to R<sup>8</sup> and to A<sup>1</sup> is through a substitutable ring carbon;

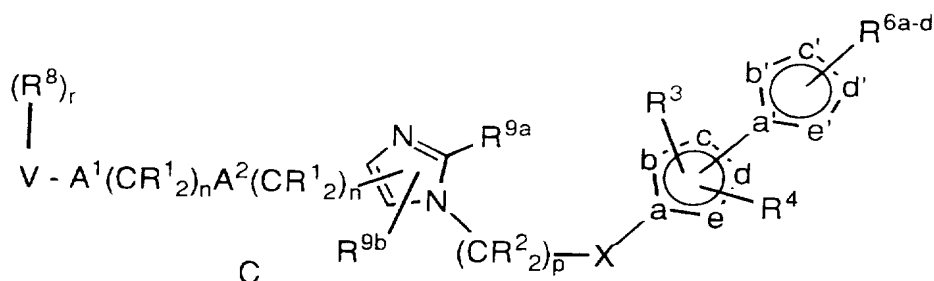
- 101 -

X is a bond,  $-\text{CH}=\text{CH}-$ ,  $-\text{C}(\text{O})\text{NR}^{10}-$ ,  $-\text{NR}^{10}\text{C}(\text{O})-$ ,  $-\text{NR}^{10}-$ , O or  $-\text{C}(=\text{O})-$ ;  
 provided that if a is N, then X is not  $-\text{C}(\text{O})\text{NR}^{10}-$ ,  $-\text{NR}^{10}-$ , or O;

- 5 m is 0, 1 or 2;  
 n is 0, 1, 2, 3 or 4;  
 p is 0, 1, 2, 3 or 4; and  
 r is 0 to 5, provided that r is 0 when V is hydrogen;

10 or a pharmaceutically acceptable salt thereof.

4. The compound according to Claim 1 of the formula C:



wherein:

15

a is N or C;

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a  
 20 is C, then at least one of b, c, d or e is independently N, NH, O or S;

a' is N or C:

25

from 0-4 of b', c', d' and e' are independently N, NH, O and S, and the remaining b', c', d' and e' atoms are independently CH, provided that if a' is C, then at least one of b', c', d' or e' is independently N, NH, O or S;

- 102 -

$R^1$  is independently selected from: hydrogen, C3-C10 cycloalkyl,  $R^{10}O-$ ,  $-N(R^{10})_2$ , F or C1-C6 alkyl;

5  $R^2$  is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C3-C10 cycloalkyl,  $R^{10}O-$ ,  $-N(R^{10})_2$ , F or C2-C6 alkenyl,
- 10 c) unsubstituted or substituted C1-C6 alkyl wherein the substituent on the substituted C1-C6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C3-C10 cycloalkyl, C2-C6 alkenyl,  $R^{10}O-$  and  $-N(R^{10})_2$ ;

$R^3$  and  $R^4$  are independently selected from:

- 15 a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl, halogen, C1-C6 perfluoroalkyl,  $R^{12}O-$ ,  $R^{11}S(O)_m-$ ,  $R^{10}C(O)NR^{10}-$ ,  $CN(R^{10})_2NC(O)-$ ,  $R^{10}_2N-C(NR^{10})-$ , CN,  $NO_2$ ,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , or  $R^{11}OC(O)NR^{10}-$ ,
- 20 c) unsubstituted C1-C6 alkyl,
- d) substituted C1-C6 alkyl wherein the substituent on the substituted C1-C6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl,  $R^{12}O-$ ,  $R^{11}S(O)_m-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  $R^{10}_2N-C(NR^{10})-$ , CN,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , and  $R^{11}OC(O)-NR^{10}-$ ;
- 25
- 30

$R^{6a}$ ,  $R^{6b}$ ,  $R^{6c}$  and  $R^{6d}$  are independently selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C3-C10 cycloalkyl, C2-C6



- 103 -

- alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN(R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- 5 c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,
- 10 R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

R<sup>8</sup> is independently selected from:

- 15 a) hydrogen,
- b) aryl, substituted aryl, heterocycle, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and
- 20 c) C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

provided that when R<sup>8</sup> is heterocycle, attachment of R<sup>8</sup> to V is through a substitutable ring carbon;

25 R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, trifluoromethyl and halogen;

30 R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

- 104 -

5  $R^{12}$  is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

$A^1$  and  $A^2$  are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR<sup>10</sup>-, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;

10 V is selected from:

- a) hydrogen,
- b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazoliny, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
- 15 c) aryl,
- d) C<sub>1</sub>-C<sub>20</sub> alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C<sub>2</sub>-C<sub>20</sub> alkenyl, and

20 provided that V is not hydrogen if  $A^1$  is S(O)<sub>m</sub> and V is not hydrogen if  $A^1$  is a bond, n is 0 and  $A^2$  is S(O)<sub>m</sub>;

provided that when V is heterocycle, attachment of V to R<sup>8</sup> and to  $A^1$  is through a substitutable ring carbon;

25 X is a bond, -CH=CH-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, -NR<sup>10</sup>-, O or -C(=O)-;

provided that if a is N, then X is not -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>- or O;

m is 0, 1 or 2;

30 n is 0, 1, 2, 3 or 4;

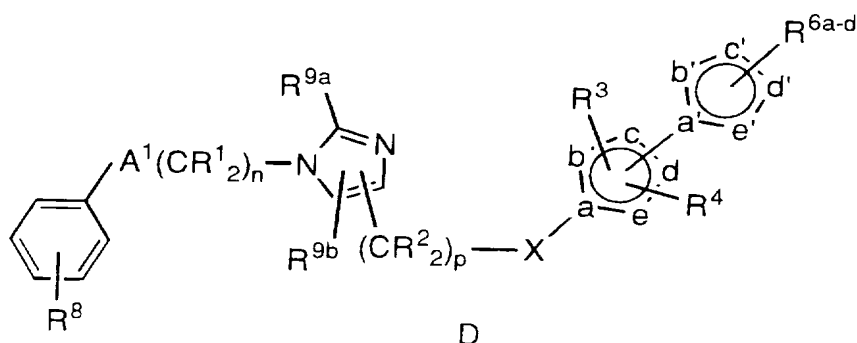
p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond, -NR<sup>10</sup>- or O; and

r is 0 to 5, provided that r is 0 when V is hydrogen;

- 105 -

or a pharmaceutically acceptable salt thereof.

5. The compound according to Claim 3 of the formula D:



5 wherein:

a is N or C:

10 from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

a' is N or C:

15 from 0-4 of b', c', d' and e' are independently N, NH, O and S, and the remaining b', c', d' and e' atoms are independently CH, provided that if a' is C, then at least one of b', c', d' or e' is independently N, NH, O or S;

20 R<sup>1</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup> is independently selected from:

- 25     a) hydrogen,  
       b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>2</sub>-C<sub>6</sub> alkenyl,

- 106 -

- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O-, or -N(R<sup>10</sup>)<sub>2</sub>;

5 R<sup>3</sup> is selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

R<sup>4</sup> is selected from H, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl and CF<sub>3</sub>;

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or

- 107 -

substituted aryl, unsubstituted or substituted heterocyclic,  
 C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl,  
 R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-,  
 R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and  
 R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

R<sup>8</sup> is independently selected from:

- a) hydrogen,
- b) aryl, substituted aryl, heterocycle, C1-C6 alkyl, C2-C6  
 alkenyl, C2-C6 alkynyl, C1-C6 perfluoroalkyl, F, Cl,  
 R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-,  
 R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and
- c) C1-C6 alkyl substituted by C1-C6 perfluoroalkyl, R<sup>10</sup>O-,  
 R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-,  
 -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;

provided that when R<sup>8</sup> is heterocycle, attachment of R<sup>8</sup> to V is  
 through a substitutable ring carbon;

R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, halogen, CF<sub>3</sub> or methyl;

R<sup>10</sup> is independently selected from hydrogen, C1-C6 alkyl, 2,2,2-  
 trifluoroethyl, benzyl and aryl;

R<sup>11</sup> is independently selected from C1-C6 alkyl and aryl;

R<sup>12</sup> is independently selected from hydrogen, C1-C6 alkyl, C1-C6  
 aralkyl, C1-C6 substituted aralkyl, C1-C6 heteroaralkyl,  
 C1-C6 substituted heteroaralkyl, aryl, substituted aryl,  
 heteroaryl, substituted heteroaryl, C1-C6 perfluoroalkyl,  
 2-aminoethyl and 2,2,2-trifluoroethyl;

A<sup>1</sup> is selected from: a bond, -C(O)-, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;

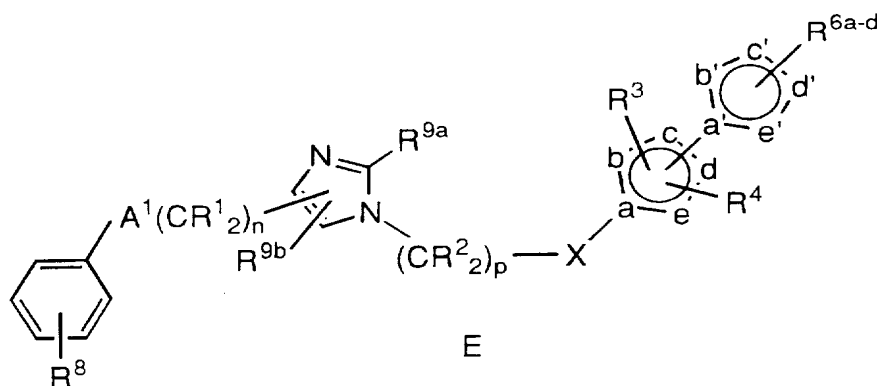
- 108 -

X is a bond,  $-\text{CH}=\text{CH}-$ ,  $-\text{C}(\text{O})\text{NR}^{10}-$ ,  $-\text{NR}^{10}\text{C}(\text{O})-$ ,  $-\text{NR}^{10}-$ , O or  $-\text{C}(=\text{O})-$ , provided that if a is N, then X is not  $-\text{C}(\text{O})\text{NR}^{10}-$ ,  $-\text{NR}^{10}-$  or O;

- 5 n is 0 or 1; provided that n is not 0 if  $\text{A}^1$  is a bond, O,  $-\text{N}(\text{R}^{10})-$ , or  $\text{S}(\text{O})_m$ ;  
 m is 0, 1 or 2; and  
 p is 0, 1, 2, 3 or 4;

10 or a pharmaceutically acceptable salt thereof.

6. The compound according to Claim 4 of the formula E:



wherein:

15

a is N or C;

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a

20 is C, then at least one of b, c, d or e is independently N, NH, O or S;

a' is N or C;

from 0-4 of b', c', d' and e' are independently N, NH, O and S, and the

25 remaining b', c', d' and e' atoms are independently CH, provided that if

- 109 -

a' is C, then at least one of b', c', d' or e' is independently N, NH, O or S;

5 R<sup>1</sup> is independently selected from: hydrogen, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F, C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup> is independently selected from:

- 10 a) hydrogen,  
b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F or C<sub>2</sub>-C<sub>6</sub> alkenyl,  
c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O-, or -N(R<sup>10</sup>)<sub>2</sub>;

15 R<sup>3</sup> is selected from:

- a) hydrogen,  
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;
- 20  
25  
30

R<sup>4</sup> is selected from H, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl and CF<sub>3</sub>;

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

- 110 -

- 5
- a) hydrogen,
  - b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
  - c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
  - d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;
- 10
- 15

R<sup>8</sup> is independently selected from:

- 20
- a) hydrogen,
  - b) aryl, substituted aryl, heterocycle, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, F, Cl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, CN, NO<sub>2</sub>, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-, and
  - c) C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>10</sup>O-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>N-C(NR<sup>10</sup>)-, R<sup>10</sup>C(O)-, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-;
- 25

provided that when R<sup>8</sup> is heterocycle, attachment of R<sup>8</sup> to V is through a substitutable ring carbon;

30

R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, halogen, CF<sub>3</sub> or methyl;

R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;



- 111 -

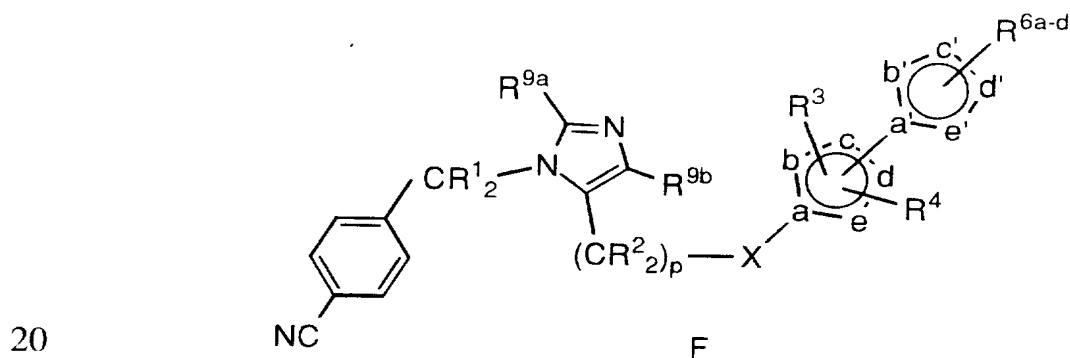
5  $R^{12}$  is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

10 X is a bond, -CH=CH-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, -NR<sup>10</sup>-, O or -C(=O)-;  
provided that if a is N, then X is not -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>- or O;

n is 0 or 1;  
m is 0, 1 or 2; and  
p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond,  
15 -NR<sup>10</sup>- or O;

or a pharmaceutically acceptable salt thereof.

7. The compound according to Claim 5 of the formula F:



wherein:

a is N or C;

- 112 -

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a is C, then at least one of b, c, d or e is independently N, NH, O or S;

5 a' is N or C;

from 0-4 of b', c', d' and e' are independently N, NH, O and S, and the remaining b', c', d' and e' atoms are independently CH, provided that if a' is C, then at least one of b', c', d' or e' is independently N, NH, O or  
10 S;

R<sup>1</sup> is independently selected from: hydrogen, C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

15 R<sup>2</sup> is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub> or F,
- c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl,  
20 heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, R<sup>10</sup>O-, or -N(R<sup>10</sup>)<sub>2</sub>;

R<sup>3</sup> is selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or  
25 substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the  
30 substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,

- 113 -

$R^{12}O-$ ,  $R^{11}S(O)_m-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  
 $R^{10}_2N-C(NR^{10})-$ ,  $CN$ ,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , and  
 $R^{11}OC(O)-NR^{10}-$ ;

5  $R^4$  is selected from H, halogen,  $CH_3$  and  $CF_3$ ;

$R^{6a}$ ,  $R^{6b}$ ,  $R^{6c}$  and  $R^{6d}$  are independently selected from:

- a) hydrogen,
- 10 b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,  $C_3-C_{10}$  cycloalkyl,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl, halogen,  $C_1-C_6$  perfluoroalkyl,  $R^{12}O-$ ,  $R^{11}S(O)_m-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  $R^{10}_2N-C(NR^{10})-$ ,  $CN$ ,  $NO_2$ ,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , or  $R^{11}OC(O)NR^{10}-$ ,
- 15 c) unsubstituted  $C_1-C_6$  alkyl,
- d) substituted  $C_1-C_6$  alkyl wherein the substituent on the substituted  $C_1-C_6$  alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic,  $C_3-C_{10}$  cycloalkyl,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl,
- 20  $R^{12}O-$ ,  $R^{11}S(O)_m-$ ,  $R^{10}C(O)NR^{10}-$ ,  $(R^{10})_2NC(O)-$ ,  $R^{10}_2N-C(NR^{10})-$ ,  $CN$ ,  $R^{10}C(O)-$ ,  $N_3$ ,  $-N(R^{10})_2$ , and  $R^{11}OC(O)-NR^{10}-$ ;

25  $R^{9a}$  and  $R^{9b}$  are independently hydrogen, halogen,  $CF_3$  or methyl;

$R^{10}$  is independently selected from hydrogen,  $C_1-C_6$  alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

30  $R^{11}$  is independently selected from  $C_1-C_6$  alkyl and aryl;

$R^{12}$  is independently selected from hydrogen,  $C_1-C_6$  alkyl,  $C_1-C_6$  aralkyl,  $C_1-C_6$  substituted aralkyl,  $C_1-C_6$  heteroaralkyl,  $C_1-C_6$  substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,  $C_1-C_6$  perfluoroalkyl,

- 114 -

2-aminoethyl and 2,2,2-trifluoroethyl;

X is a bond, -CH=CH-, -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>C(O)-, -NR<sup>10</sup>-, O or -C(=O)-;

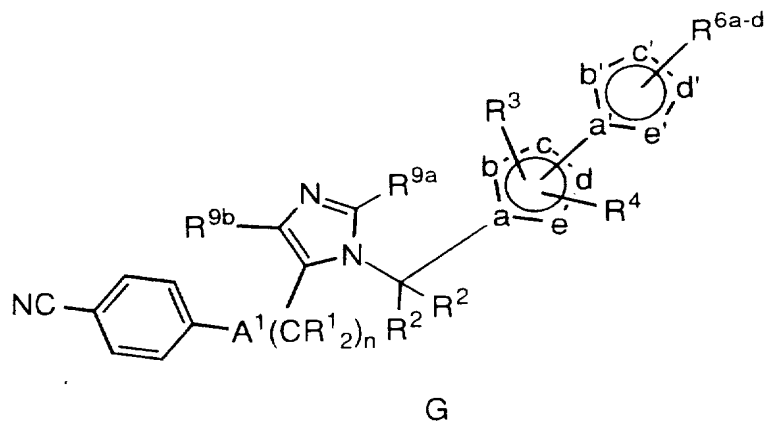
5 provided that if a is N, then X is not -C(O)NR<sup>10</sup>-, -NR<sup>10</sup>- or O;

m is 0, 1 or 2; and

p is 0, 1, 2, 3 or 4;

10 or a pharmaceutically acceptable salt thereof.

8. The compound according to Claim 6 of the formula G:



wherein:

15

a is C;

from 0-4 of b, c, d and e are independently N, NH, O and S, and the remaining b, c, d and e atoms are independently CH, provided that if a

20

a' is N or C;

from 0-4 of b', c', d' and e' are independently N, NH, O and S, and the remaining b', c', d' and e' atoms are independently CH, provided that if

25

- 115 -

a' is C, then at least one of b', c', d' or e' is independently N, NH, O or S;

5 R<sup>1</sup> is independently selected from: hydrogen, R<sup>10</sup>O-, -N(R<sup>10</sup>)<sub>2</sub>, F, C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup> is independently selected from:

- 10 a) hydrogen,  
b) aryl, heterocycle or C<sub>3</sub>-C<sub>10</sub> cycloalkyl,  
c) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by aryl, heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, R<sup>10</sup>O-, or -N(R<sup>10</sup>)<sub>2</sub>;

R<sup>3</sup> is selected from:

- 15 a) hydrogen,  
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,  
20 c) unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
d) substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;  
25  
30

R<sup>4</sup> is selected from H, halogen, CH<sub>3</sub> and CF<sub>3</sub>;

R<sup>6a</sup>, R<sup>6b</sup>, R<sup>6c</sup> and R<sup>6d</sup> are independently selected from:

- a) hydrogen,

- 116 -

- 5           b)    unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, NO<sub>2</sub>, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, or R<sup>11</sup>OC(O)NR<sup>10</sup>-,
- c)    unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- 10          d)    substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>12</sup>O-, R<sup>11</sup>S(O)<sub>m</sub>-, R<sup>10</sup>C(O)NR<sup>10</sup>-, (R<sup>10</sup>)<sub>2</sub>NC(O)-, R<sup>10</sup><sub>2</sub>N-C(NR<sup>10</sup>)-, CN, R<sup>10</sup>C(O)-, N<sub>3</sub>, -N(R<sup>10</sup>)<sub>2</sub>, and R<sup>11</sup>OC(O)-NR<sup>10</sup>-;

15

R<sup>9a</sup> and R<sup>9b</sup> are independently hydrogen, halogen, CF<sub>3</sub> or methyl;

20       R<sup>10</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R<sup>11</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

25       R<sup>12</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> aralkyl, C<sub>1</sub>-C<sub>6</sub> substituted aralkyl, C<sub>1</sub>-C<sub>6</sub> heteroaralkyl, C<sub>1</sub>-C<sub>6</sub> substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

30       A<sup>1</sup> is selected from: a bond, -C(O)-, O, -N(R<sup>10</sup>)-, or S(O)<sub>m</sub>;

m is           0, 1 or 2; and

n is           0 or 1;

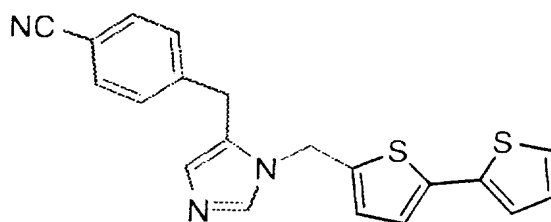
- 117 -

or the pharmaceutically acceptable salts thereof.

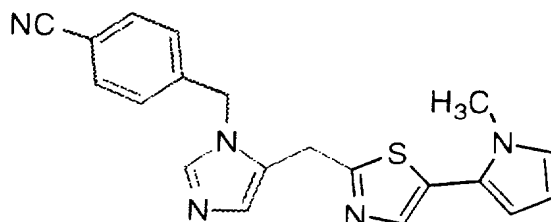
9. A compound which inhibits farnesyl-protein transferase which is:

5

1-(5-(Thien-2'-yl)thien-2-ylmethyl)-5-(4-cyanobenzyl)imidazole



10 1-(4-Cyanobenzyl)-5-(5-(1-methylpyrrol-2-yl)-thiazol-2-ylmethyl)imidazole



or a pharmaceutically acceptable salt thereof.

15 10. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

20 11. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 3.

12. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 4.

- 118 -

13. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 9.

5

14. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

10

15. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 11.

15

16. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.

20

17. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 13.

25

18. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

19. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 11.

30

20. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.



- 119 -

21. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 13.

5                   22. A method for treating neurofibromin benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

10                   23. A method for treating blindness related to retinal vascularization which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

15                   24. A method for treating infections from hepatitis delta and related viruses which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

20                   25. A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

25                   26. A method for treating polycystic kidney disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

                    27. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier.

30                   28. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/06259**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : A61K 31/415; C07D 409/06

US CL : 514/397; 548/315.1

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/397; 548/315.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2,468,168 A (BYWATER et al) 26 APRIL 1949 (26/04/49), see entire document, especially column 1.	1-28, parts

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

11 JUNE 1997

Date of mailing of the international search report

18 JUL 1997

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ROBERT W. RAMSUEER

Telephone No. (703) 308-1235

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/06259

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-28, parts  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
  
Please See Extra Sheet.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/06259

## BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

The multitude of variables and their permutations and combinations (e.g. V,A1,A2,W,X,R1,R2,R3,R4,R5,a,b,c,d,e,n,the provisos,etc.) result in claimed subject matter that is so broad in scope that it is rendered virtually incomprehensible and thus no meaningful search can be given. Note also that the claimed subject matter lacks a significant structural element qualifying as the special technical feature that clearly defines a contribution over the art. The subject matter claimed contains only variables and thus does not contain a special technical feature which defines a contribution over the prior art. Therefore, the first discernible invention as found in Example 1,(the compound therein, the pharmaceutical composition therewith, and the method of treating colorectal carcinoma therewith) has been searched.